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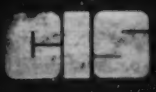

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THE HUMAN GENOME PROJECT

HEARING

BEFORE THE

SUBCOMMITTEE ON
ENERGY RESEARCH AND DEVELOPMENT

OF THE

COMMITTEE ON
ENERGY AND NATURAL RESOURCES
UNITED STATES SENATE

ONE HUNDRED FIRST CONGRESS

SECOND SESSION

ON THE

HUMAN GENOME PROJECT

JULY 11, 1990

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THE HUMAN GENOME PROJECT

WEDNESDAY, JULY 11, 1990

U.S. SENATE,
SUBCOMMITTEE ON ENERGY RESEARCH AND DEVELOPMENT,
COMMITTEE ON ENERGY AND NATURAL RESOURCES,
Washington, DC.

The subcommittee met, pursuant to notice, at 9:35 a.m., in room SD-366, Dirksen Senate Office Building, Hon. Wendell H. Ford, presiding.

OPENING STATEMENT OF HON. WENDELL H. FORD, U.S. SENATOR FROM KENTUCKY

Senator FORD. Good morning, ladies and gentlemen. Welcome to the human genome project hearing this morning.

First, let me congratulate Senator Domenici for encouraging us to hold this hearing. Senator Domenici has been a leader in the formulation of the human genome project. His staff has provided us with invaluable help in organizing this hearing on the status of the project.

I am not an expert on research on the human genome. I could not sound like one if I wanted to.

The genome studies that are underway are fundamental to understanding the role of genetics in human health. It is one of the amazements of our age that we have the capability to delve so deeply into the very structure of living things.

Our role in Congress is to assure ourselves that these research efforts are well conceived and competently directed. If this assurance is provided we must search for the funds to support the work.

These funds continue to be limited. The choices that are made in allocating research dollars are hard choices. I am concerned that the percentage of approved biomedical research grants that actually receive funds is dropping. This is a bad signal to be sending to our young people who are entering science. I hope the witnesses here today can assure me that the human genome project is not contributing to this problem by absorbing the available new money for the field.

The debate on the human genome program also has echoes of the "big science" versus "little science" controversy we have seen in this Subcommittee with the superconducting supercollider project I hope we can discuss the extent to which this is an aspect of the project. With that opening statement, I am very pleased that Senator Domenici is here, and Pete, if you have any statement we would be glad to have it at this time.

STATEMENT OF HON. PETE V. DOMENICI, U.S. SENATOR FROM NEW MEXICO

Senator DOMENICI. Thank you very much, Mr. Chairman. First, let me thank you as Chairman of the Subcommittee for calling this hearing. I have a statement that expresses my views and a little bit of the history. I would like that to be made a part of the record.

Senator FORD. Without objection, so ordered.

Senator DOMENICI. A number of research groups and eminent scientists have written to me with reference to this hearing, and eventually I will place their indications of support in the record, but I would like to open my comments with a quote from one of them, from Emory University School of Medicine, because a few words by one of the scientists there does a better job than I in explaining this program, and so I would open by saying: "The goals of the human genome project will revolutionize human biology and medicine as well as provide technological development that will rival that of the early manned space program."

Essentially, Mr. Chairman, since our initial Federal investment of about $5.5 million at DOE in 1987, we have allocated about $166 million for this comprehensive mapping and sequencing effort. For this year, the Administration has requested $47 million at DOE and $108 million for NIH. Reports by the National Academy of Science, and the Office of Technology Assessment, have recommended eventual annual funding of about $200 million for 15 years. Since this Committee first held its hearings on this project, and we have jurisdiction over some of the most important research labs in the project, it is very important that we conduct this oversight hearing.

We started this effort by moving some legislation to establish a strong national genome program and to provide some coordination between the DOE and NIH, and to assure private sector involvement so that the United States could take ultimate advantage of the investment.

This hearing, Mr. Chairman, from my standpoint should accomplish two things: to see where we have come over the past three years and assess the feasibility of where we are going. The DOE has a strong history in this activity and the National Institutes of Health, obviously, do also. They are working together.

There are many compelling reasons that we should support this initiative, and I hope before we are finished we will be able to dispel any notion that this project is taking money away from small science and small biomedicine and biomedical research. I think we have numbers to prove that this program is not the cause of whatever complaints or elements we might have about not having more grants out there.

This project—and let me just conclude with this—promises to create a genetic map within five years to help locate all 100,000 genes in a human and to find a complete human DNA sequence in 15 years. We might, through this, deliver a tool to our researchers—and imagine this—that could permit them to go after 3,500 genetically-related diseases.

I have one letter of testimony that I would like to put in now, and then we will reserve the rest. I think last year the Multiple Sclerosis Society had a great celebration. They were able to make

the breakthrough with reference to multiple sclerosis genetically. They support the genome project.

They have succeeded in their one problem, but I would suggest that they are very prudent in that they spent $120 million, it is estimated, from the beginning of that research until they isolated that particular genetic relationship which might permit a cure or at least significant amelioration of the symptoms. Think of that. $120 million for one, and we may very well, over five years, with about $200 million a year, be able to deliver a map of most of this to the scientists of America and the world.

I am very excited about this program, and I am delighted that it has broad-based support. The Industrial Research Institute took a poll, you might be interested to know. We occasionally refer to the superconductor supercollider, the space station, and strategic defense initiative. They stated the number one project should be the human genome initiative. Fifth should be superconducting supercollider; fourth, SDI; third, space station, and second the hypersonic project. There are numerous groups of scientists and experts in the field that clearly indicate this should be the No. 1 project.

I want to close with these remarks, Mr. Chairman. The next 30 years will see more scientific breakthroughs of a fundamental nature in the world than in all of human history. I believe that is because we have added the capacity of the computer to the mind of man, and thus exponentially accelerated the capability of man's brains and intelligence to make breakthroughs. I am very hopeful that one of those stupendous breakthroughs will be the mapping of the human genome.

Thank you very much. I look forward to the hearings.

[The prepared statement of Senator Domenici follows:]

STATEMENT BY SENATOR PETE V. DOMENICI

Hearing on the Human Genome Initiative
Sub-Committee on Energy Research and Development
9:30 AM, July 11, 1990

Mr. Chairman, I would like to thank you for holding this hearing to review the Federal government's human genome program. This is one of the most exciting and promising programs that we presently support. Over the past several years the Federal government's investment in mapping and sequencing the human genome has grown considerably. Since 1987, when an initial $5.5 million was appropriated to the Department of Energy for the human genome initiative, Congress has allocated nearly $166 million for this project. In fiscal year 1991, the Office of Management and Budget has requested $47.8 million at DOE and $108 million at NIH for the Human Genome Initiative.

Two separate reports issued in 1988 by the National Academy of Sciences and the Congressional Office of Technology Assessment called for a final budget of $200 million per year for 15 years. This budget will allow the scientists working within the human genome initiative to completely map and sequence all of the DNA in a human. This knowledge promises revolutionary advances in medicine as well as providing a strong boost to the

young American biotechnology industry.

This Sub-Committee played a key role in the beginning of the human genome initiative. This was the first Committee in Congress to explore the potential for human genome mapping efforts to increase the quality of human life. In 1987, the Subcommittee on Energy Research and Technology held a workshop in Santa Fe, New Mexico, and a hearing in Washington D.C., examining the role of the Department of Energy in this research. At that time I introduced S. 1480, "The Department of Energy Cooperative Research Initiatives Act", which called for the creation of an administrative structure for the Human Genome Initiative, and helped to lay the ground work for the highly important investment we are now making in human genome research.

The Department of Energy has a strong history of working in molecular biology research. The national laboratories house the computer data base of DNA sequence (Genbank at Los Alamos), serve as the major source of isolated DNA chromosomes for biological research around the country, and just two years ago DOE scientists took the first images of DNA with an advanced microscope. The DOE has also managed to form a strong working relationship with the National Institutes of Health on the human genome initiative. This spirit of cooperation is written into the "Memorandum of Understanding" signed by the two agencies in 1988.

The national laboratories have a unique multi-disciplinary excellence which will greatly aid in the human genome initiative. The national laboratories also have a strong tradition of managing large scientific programs which will be useful in a project as large and diverse as the genome effort. We have with us today the heads of the three national laboratories involved in human genome research. I look forward to hearing of their progress on the initial stages of the program.

Three years ago this Sub-Committee held the first hearing on the human genome initiative. Since then the three DOE genome centers have been established, the NIH has begun to select its own genome centers, and a joint DOE-NIH committee has issued a 5 year plan which carefully lays out plans for future research. Today I am anxious to hear from both Dr. Watson and Dr. Galas on each agency's progress on the goals that they have set.

There have been some concerns raised about the implications of the human genome initiative. There have been those in the biomedical community who seem to believe that the human genome initiative will drain funds from other essential research. These concerns, I believe, are unfounded. Biomedical funding has gone up consistantly during the past decade, during a time of particularly tight budgets. Further, funding at the N.I.H. for the human genome initiative would clearly not be there now if it were not for this very important project. There are simply to many other important Federal concerns in Labor Health and Human

Services appropriations budget. Finally, questions have been raised about ethical problems that may be created by genome research. These concerns should be taken seriously, and we look forward today to hearing about them.

In fact, there are many compelling reasons why the Federal government should fund the human genome initiative. The NIH presently spends over $300 million dollars per year in small grants that support mapping and sequencing work of DNA. Further, the Cystic Fibrosis Foundation estimates that $120 million was spent to find the single gene responsible for this terrible disease. The human genome initiative, however, promises to create a genetic map in the first five years that will help locate all 100,000 genes in the human and to find the complete DNA sequence in 15 years. This new resource of genetic information will prove invaluable to future researchers to continue their dramatic advances in medical research and hopefully to find cures for the more than 3500 identified genetic-related diseases.

The medical promise of advances made in biotechnology research continue to grow. A recent article in the New England Journal of Medicine reported on promising studies involving a new biotechnology drug called human growth hormone produced by Genentech. The studies suggest that the drug may not only help prevent dwarfism but also aid in slowing the aging process. Further, the first human gene therapy trials are nearing approval

at the NIH. These particular treatments are aimed at curing the debilitating disease that caused David the "Bubble Boy" to spend most of his short life confined to a plastic life support prison. Finally, the great discovery by Francis Collins of the gene for Cystic Fibrosis has already led to promising advances in the search for a cure for that dreaded disease. We can hope for this same progress for other diseases as the human genome initiative moves forward to map and identify all of the human genes.

The biotechnology industry in this country is young but growing quickly. In 1989 the biotechnology industry had a combined revenue of over $1.2 billion, a %33 percent increase over the previous year. Many of the products produced are sold for exports. Many of these companies, including Cetus, Genentech, and Perkin-Elmer are already collaborating with the human genome initiative. Future technological advances developed by the human genome initiative will greatly aid in allowing the biotechnology industry to continue to grow and provide both new jobs and medical products.

Support for the human genome initiative is broad based. Originally conceived of by scientists in the DOE, the proposal for a concerted Federal effort to study human DNA received strong endorsements in reports issued by the National Academy of Sciences and the Office of Technology Assessment. It also enjoys the support of the President and his science advisor, Dr. Bromely. In a recent poll conducted of over 105 companies by the

Industrial Research Institute, the human genome initiative was ranked number one over four other large Federal science projects in business promise. Forty two members of the National Health Council have stated that they support Federal support for the human genome initiative.

I believe that the Human Genome Initiative is one of the most important federal research programs in this year's budget. It seeks nothing less than to find the genetic basis for many of the major diseases that effect modern society including cancer, heart disease, Alzheimer's disease, and Cystic Fibrosis. It is in the best interest of this nation's health care system and economic prosperity to ensure that the Human Genome Initiative reach its full level of funding as soon as possible. I look forward to today's testimony as we examine how the human genome project is being administered.

Senator FORD. Thank you very much, Senator Domenici.

Our first witnesses today are Dr. James Watson, Director of the National Center for Human Genome Research of the National Institutes of Health, and Dr. David J. Galas, Associate Director, Health and Environmental Research, the Office of Energy Research, Department of Energy, and accompanying Dr. Watson will be Dr. William Raub, Acting Director of the National Institutes of Health.

So Dr. Watson, we look forward to your testimony and ask that you proceed.

Senator DOMENICI. Mr. Chairman, would you permit me. You cannot help it. I said multiple sclerosis. I meant cystic fibrosis. The $120 million and the breakthrough, it was not multiple sclerosis, but cystic fibrosis that celebrated the breakthrough. Thank you, Mr. Chairman.

Senator FORD. It is always nice to know an individual can admit a mistake.

Senator DOMENICI. I read the wrong letterhead. [Laughter.]

Senator FORD: Dr. Watson.

STATEMENT OF DR. JAMES D. WATSON, DIRECTOR, NATIONAL CENTER FOR HUMAN GENOME RESEARCH, NATIONAL INSTITUTES OF HEALTH, PUBLIC HEALTH SERVICE, DEPARTMENT OF HEALTH AND HUMAN SERVICES, ACCOMPANIED BY DR. WILLIAM F. RAUB, ACTING DIRECTOR

Dr. WATSON. Senators Ford and Domenici, thank you for the opportunity to appear in front of you. I would like to ask that my formal testimony be placed in the record.

Senator FORD. It will be included in the record, Doctor.

Dr. WATSON. I will speak very briefly, believing it is better if I respond to specific questions from you.

Senator FORD. We thank you and we appreciate that.

Dr. WATSON. I am very pleased to be here with a fellow group from the Department of Energy. Together, our agencies have developed a five-year plan for proceeding with the human genome mapping and sequencing effort. This plan appeared several months ago. It was the result of deliberations which began roughly a year ago. We intend to upgrade this plan every year. Not that we think we have made mistakes, but because we will get new information and we do not want to be trapped into a course of action which does not take into account new facts.

I will briefly indicate the major activities which are being done, really, by both groups. Dr. Galas will have his own particular emphasis, but I am trying to indicate that we are working together, not that there is an NIH program and that there is a DOE program. I think it would be very counterproductive if we were really competing with each other. It is a big project, and I think we can work together very effectively.

The NIH, I should point out, feels that it really has to be part of this program, because so many diseases have a genetic component. That is really why we are involved. Cancer has enormous genetic components. Diabetes has genetic components. Many mental diseases have genetic components, and we want to find these compo-

nents. We are still dealing, in many cases, with diseases for which we only have Band-Aids and no good pills. I think that if we can find out why there is a genetic predisposition to so many diseases, we will be in a much better position to do the final research necessary to, in some cases, banish these diseases from the human vocabulary.

Genetics is at the heart of the NIH mission and will continue to be at the heart of it. What we really want is to find genes, and to do that we have to prepare genetic maps. That is the highest priority of our program. We want to get very high-resolution genetic maps so that if you have a family pedigree you will be able to assign a gene to a chromosome, or in the case of some diseases, assign several genes.

This is a technique which only became possible roughly seven years ago. When we began to get enough genetic markers that you could assign them, Huntington's disease was assigned to chromosome four and cystic fibrosis was assigned to chromosome seven. Many other genes now have been assigned to specific chromosomal locations.

Now, once we know the rough location of the gene on the chromosome we want to be able to clone the gene. That brings us to the second objective of our program—to gather pieces of all the DNA of a given chromosome. We call this an ordered library. Once Francis Collins knew that the cystic fibrosis gene was on chromosome seven, his objective was to get that exact piece of DNA which carried the gene.

In the absence of our human genome program, this was a very tricky job. And as you mentioned, Senator, the Search for the cystic fibrosis gene took seven years and cost some $100 million. We want to speed up this process for people working on other diseases by having these pieces of DNA available for all investigators. An ordered library is an objective which we think we can achieve for all the 24 different chromosomes over the next five years.

The third thing we eventially wish to do is determine the entire human DNA sequence. In the case of the cystic fibrosis gene, Francis Collins sequenced it and found a difference, a mutant form of the gene which gave rise to the disease. Sequencing is currently an expensive task. It costs between $5 and $10 a base pair of DNA, and if you multiply that by the total size of the genome, which is roughly 3 billion base pairs, that would give you $30 billion.

When the project was first proposed, and people thought if would cost $30 billion, they said no, you cannot do it. It would take away money from everything else. But we think we can reduce the cost, so a major objective of ours over the next five years is to see if we cannot bring down the cost by a factor of ten. We are doing this by giving out a variety of grants to try and develop new technologies which would reduce the cost of sequencing.

Senator DOMENICI. So you are proceeding with the mapping while you are experimenting with better ways and cheaper ways to do the sequencing that follows?

Dr. WATSON. Yes. We can do the mapping now. We knew it was probably possible three years ago and everything that has happened since then has said that we can do it faster. There is absolutely no doubt that we can do the mapping. So, let us get on with

it. We want the markers to find the gene for manic depressive disease. We thought we had the gene. We now realize we do not, but we want it fast, so that is why we want the markers.

The fourth part of our program is that, as we accumulate this DNA sequence data, we are going to have to handle it. We are going to have to really know how to use computers. You mentioned this whole program would not be possible without computers. Now that we have them, we really need to put people together with computers so that this information can be effectively used.

The fifth part of our program is that, already, the existence of genetic differences, genetic diseases, creates ethical and legal problems. We have set up a very effective committee, a joint NIH-DOE committee, to deal with the ethical, legal and social issues of the genome program.

Senator DOMENICI. Could you pull the mike up a little closer, doctor?

Dr. WATSON. We have created a jount NIH-DOE committee to deal with ethical, social and legal issues. I think you may have read an article in the Wall Street Journal on Monday concerning complications involving insurance for people who are known to have genetic disease. That is, if you come from a family with Huntington's Disease, the insurance company may not believe that you should get an insurance policy. Well, this is a pretty awful thing for the individual, and it is also difficult for the insurance industry.

So there are already existing ethical issues, and more will come into existence. We want to create an active program where we bring together all the diverse groups which are going to be affected by these issues. And I am sure these issues will come in front of Congress in many different ways. They already exist and we need to start discussing them.

I am very pleased with our ethics committee. It is chaired by Nancy Wexler, president of the Hereditary Disease Foundation. And in our office at NIH, we have appointed Eric Juengst as head of our bioethics program. I think we are moving very successfully.

Another aspect of our program concerns technology development and transfer. DNA is going to be more and more important in all aspects of life. New technologies and instrumentation are going to be commercially important. Both will be critical to getting important data and developing new drugs.

We want to work very hard to see that the fruits of this program benefit the American people and its industry. That is very strong in our minds. One reason we believe we should proceed with this program is that, if we did not proceed, we would be losing an enormous opportunity to use the American spirit to develop important new forms of technology.

The last thing I should mention is that a program of this importance is not going to be left to the United States. Other nations are equally interested in the human genome, and there are programs in the U.K., France, Soviet Union, and Japan. It is very important that we somehow determine a way in which we can collaborate and share information—and at the same time preserve America's national interest.

It is important to strike the proper between these two issues. One issue concerns the development of the technology and instru-

mentation that will be needed for the project. The other concerns who is actually given the instruments and who is going to do the work to produce the sequence. It is my hope that the final working out of the sequences can in some way be shared between different countries. There are different ways of looking at these issues, but deep down, I think all of us want to share this information because it is related to our health. The idea of not sharing it, that we would keep someone else in another country from possibly solving a disease which also affects Americans would be repugnant to me and to everyone else.

But we must also strive to maintain the United States' competitive position in biotechnology. And with that, I will thank you.

[The prepared statement of Dr. Watson follows:]

FOR RELEASE ON DELIVERY

Testimony by

Dr. James D. Watson, Director

National Center for Human Genome Research

National Institutes of Health

Public Health Service

Department of Health and Human Services

Hearing on the Human Genome Project

Before the

Subcommittee on Energy Research and Development

Committee on Energy and Natural Resources

United States Senate

July 11, 1990

Mr. Chairman and Members of the Subcommittee:

Thank you for the opportunity to present testimony on behalf of the National Center for Human Genome Research of the National Institutes of Health (NIH). The U.S. Congress is a very important partner in the Human Genome Project and we welcome the opportunity to brief you personally on a program of immense importance to us all.

As you know, I became convinced several years ago that the Human Genome Project was a bold, important, and vital new component of our country's biological/biomedical research effort. Today, as I see the rapid rate at which our science is converting the promise of three years ago into the reality of today, I am more convinced than ever of the significance of this program. Still there are scientists who do not understand the objectives and strategies of our program, and the promise that it holds even for their own work. We clearly must improve our educational and outreach activities and so I am particularly pleased to have this opportunity to describe the Human Genome Project to you.

What is the Human Genome Project?

More and more, scientists are identifying genetic causes or genetic components of an ever-increasing number of diseases. At the same time, an increasing fraction of the budget of NIH and related agencies in the Department of Health and Human Services is devoted to finding the genes involved in major health problems. For example, the National Institute on Aging is interested in the genetic basis of Alzheimer's Disease, while the National Institute of Mental Health has begun a concerted program to find

genes involved in several serious psychiatric disorders. Recently, the identification of the cystic fibrosis gene was heralded as a major breakthrough by the National Institute of Diabetes and Digestive and Kidney Diseases. Almost all of the National Institutes of Health support research into the identification of the genetic basis of human disease.

While these gene searches are considered to be of very high priority, they are arduous and expensive. A recent report on the isolation of a gene for Alport Syndrome, which is characterized by progressive loss of hearing and kidney function, is an example of the complexity of the job -- the work that eventually led to the recent identification of the gene for Alport Syndrome began in 1949! The successful identification of the cystic fibrosis gene provides another case: it required 7 years and some $100 million to pinpoint that gene. Similar sums are being spent to find other disease genes. It is no exaggeration to say that only the "easy" genes have been found so far. The more "difficult" ones may never be found with currently available methods. The search for disease genes will continue, as it is information critical to the health of all of us. Because these genes are so important, the question is how can we find them in the most efficient and cost-effective way. The Human Genome Project is a coordinated and focused effort to work toward this goal.

Dr. Francis Collins, one of the co-discovers of the cystic fibrosis gene, put it this way:

> The amount of effort required to identify this gene was almost overwhelming, and yet cystic fibrosis is actually an example of a more straightforward and

solvable problem than more difficult genes such as Alzheimer's disease, cancer, or schizophrenia. Without the data which the Human Genome Project will generate, it is difficult for me to conceive that we will make much headway in the identification of genes for common disorders such as these. Thus, the Human Genome Project is not just a convenient alternative -- it is essentially the only viable approach to identify the major genetic influences which affect the health of all of us.

Only a few thousand human genes have so far been mapped to human chromosomes. Only a handful of these have been isolated and sequenced. Most of the human genome is unexplored territory. The Human Genome Project is designed to chart this territory, identify the major landmarks, and build the system of pathways that will enable researchers to reach their targets rapidly, so that they can concentrate on the next phase, namely studying the function of important genes and developing improved diagnostics, treatments and cures.

At the estimated cost of $3 billion for the entire project, we would spend only $30,000 per gene, assuming there are 100,000 genes in the human genome. This will save years of work and many millions of dollars for each gene that is isolated compared to using current methods. Research funded by the project will provide immensely valuable information about the genetics of other organisms -- yeast, Drosophila (the fruitfly), C. elegans (the roundworm), bacteria, and the mouse. The information we obtain from

the genomic analysis of these organisms will directly help us to understand the human genome and human biology. We will also train highly skilled interdisciplinary investigators, and develop databases and repositories of valuable information and materials that will be accessible to all who need it. The societal implications of the availability of this new knowledge are now being studied and we will develop proposals for how it can be used in the most beneficial ways while, at the same time, protecting individuals. Those who feel the cost of the Human Genome Project is too high have failed to consider the cost of not doing the project in a coordinated way. Doing genetic mapping in the business-as-usual manner is much slower and more expensive and does not take the best advantage of our ability to use genetic knowledge to improve human health.

The Human Genome Project is about developing new information, resources, and technologies.

Mr. Chairman, we have developed a plan for the first five years of the Human Genome Project, which I would like to describe to you briefly. The plan was produced jointly with the Department of Energy and, together with them as well as our other partners, we have already begun to work to achieve the goals we have set in these first five years.

. .apping the Human Genome

Mapping is the process of determining the position and spacing of genes, or other genetic markers, on the chromosomes. There are basically two types of maps, genetic and physical, which differ in the methods used to construct them and in the unit that is used to measure the distance between genes. We intend to create more useful genetic and physical maps of all human chromosomes. Such maps, and the materials on which they are based will allow scientists to quickly locate a gene and then to rapidly find the piece of DNA containing that gene.

As a first step, we plan to create a genetic map of informative, high-quality "index" markers spaced evenly along each of the chromosomes. These markers, many of which already exist, will immediately make finding disease genes more efficient than it is today. They will be indispensable to more detailed mapping and sequencing of the chromosomes. We will focus on storing the markers in a central place, making them available to all scientists. We will continue to fill in the regions of the genome in which such markers are missing. This plan has been enthusiastically received by the scientific community. At least one scientist has agreed to organize these markers for each chromosome, and we have received expressions of interest from our European partners to join us in this effort. Within two years, we hope to have this map completed and the markers available from a central source.

Most of our funds at this stage are being spent on chromosome mapping. We know how to do it well and there are immediate benefits for other scientists. Remarkable progress has been made in the past few years in the technology available for physical mapping. One example is the yeast artificial chromosome, or YAC. This vector system, developed at Washington University School of Medicine in St. Louis, allows the isolation and manipulation of DNA in pieces from 5 to 20 times larger than had previously been possible. These larger pieces of DNA make it easier to assemble them into a complete map. Washington University researchers have used the YAC system to create a "library" of DNA fragments containing the entire human genome. This library is now being widely distributed across the country and has immensely improved mapping strategies in a number of laboratories.

Recently a group of four NIH and DOE-supported scientists proposed a new common language system for collecting information from physical mapping projects. The elements of this new language are referred to as "sequence-tagged-sites" or STS's. Use of STS's will allow the data from diverse physical mapping techniques to be more effectively integrated into a single map. The STS proposal also reduces the need for large, expensive central repositories of DNA, as the information about STS identities can be stored in a public database and used by a scientist in any laboratory to regenerate a desired piece of DNA easily.

Sequencing the Human Genome

Sequencing is the process of determining the order of the subunits, called nucleotides, in a DNA molecule. Sequencing DNA is a tool that is essential to modern biological science. It has been estimated that a typical molecular biology lab studying the yeast genome spends 25 to 30% of its resources on sequencing. Thus, sequencing costs are currently a major component of the cost of research in some fields. Significantly reduced sequencing costs will be an important spin-off of the Human Genome Project and one that will be available to all labs, large or small.

Because the cost of sequencing is currently so high, only a small fraction of our funds is supporting sequencing -- considerably less than 10% now and probably not more than 10% during the first five years. The current investment is designed to bring the cost of DNA sequencing down so that when we have completed the physical chromosome maps, we can proceed to sequence the DNA in a less expensive way. We will not support sequencing the DNA of an entire human chromosome until the cost is 50 cents or less per base pair, which is ten times less than it costs today. New technologies will reduce not only the cost of sequencing but the amount of labor required by current sequencing methods. Automating the entire process will eventually bring this technology into every laboratory.

We are taking two approaches to bring the cost of sequencing down. The first is to develop novel methods. One example relies on a mass spectrometry-based instrument

that is being developed at a small company in California under support from the National Center for Human Genome Research. Because mass spectrometry has been widely used in labs for decades, this method holds great promise for improvements in cost, speed, and accuracy. The second approach supports some pilot projects in which scientists will scale up sequencing efforts by a factor of five to ten to improve the technology and efficiency of large-scale sequencing. The goal is to assess the effects of economies of scale and organization in order to improve the efficiency of large-scale sequencing. Only sequencing at this scale will get the entire human genome done. These pilot projects will sequence DNA with known biological significance, so we can learn about the biology of DNA while improving sequencing methods.

One pilot project will be to sequence the DNA of the roundworm, C. elegans. The physical map of the DNA of this worm is almost complete and scientists are poised to begin the sequencing. Almost every gene that has been identified in C. elegans has a human counterpart. Thus, as we find the C. elegans genes, this information can immediately be used to search for the comparable human genes. The sequencing of C. elegans DNA will be done jointly with scientists in England, and the cost will be shared between the U.K. and the NIH.

The Human Genome Project is about training young scientists.

In the course of the Human Genome Project, large numbers of scientists will be trained in the newest methods of molecular analysis. We are also establishing training

programs in which young scientists can develop the interdisciplinary skills that will be critical to work at the forefront of science in the next century. These scientists will help keep U.S. academia and industry competitive in a field in which the U.S. now enjoys pre-eminence.

We are pleased that highly talented individuals, understanding the tremendous potential of the genome effort, are participating in the Genome Project and have attracted students and post-doctoral fellows to their laboratories for training. The opportunity to analyze and decode the messages locked away in human DNA is an attractive challenge to many bright scientists.

The Human Genome Project is about technology and technology transfer.

The Human Genome Project will produce much valuable new technology, indeed it has already done so. Some of the technology will be biological while other advances will be in the areas of new instrumentation, medical tests, therapies for disease, and means of information acquisition, storage, retrieval, and distribution.

Spurring technology development has not only scientific but economic benefits as well. The biotechnology industry will benefit from the trained manpower, data, and techniques developed by the Human Genome Project and will generate many useful applications of the new knowledge that is produced. Synthesizing and manipulating biological proteins in the laboratory, however, ultimately depends on knowing the

sequence of the gene that encodes the protein. Rapid transfer of technology developed under the Human Genome Project to industries that can develop medically and economically useful applications is a major goal of the Genome Project. The U.S. biotechnology industry considers the Genome Project critical for maintaining and increasing U.S. competitiveness.

The National Center for Human Genome Research and the NIH Office of Technology Transfer are planning to sponsor a technology transfer conference this December. The intent of this one-day conference will be to bring together key representatives from the biotechnology industry, pharmaceutical companies, and government officials to discuss the role of the government in the transfer of technology associated with the NIH Human Genome Project. This exchange should provide valuable insight into how best to promote and facilitate technology transfer for the NIH Genome Program. Because of the importance we assign to this area, we are currently recruiting an individual who will take primary responsibility for technology transfer and be our liaison to the biotechnology industry.

The Human Genome Project is about international cooperation and economic competitiveness.

Other countries view the U.S. Human Genome Project as the worldwide leader in genome research and are fashioning their plans and programs with much consideration of what we are doing. Many countries have now funded their own genome programs,

including Italy ($2 million per year), the United Kingdom ($5.9 million), the U.S.S.R. ($2.0 million), Japan ($6.3 million), and the European Community ($8 million). These amounts are not directly comparable to the U.S. budget because they represent add-on funds for laboratories that are for the most part already funded for their basic operating costs. We expect these programs to grow and additional countries to join in this international research effort. France, for example, intends to announce a program soon. These international partners are critical to the success of the Human Genome Project, and such collaboration should reduce the cost of the Genome Project to the United States.

A major challenge is to strike the proper balance between the necessity for international cost-sharing and scientific collaboration and the need to promote the United States' competitive position in biotechnology. The financial and scientific benefits of international cooperation in the analysis of the human genome are unquestionable, but we want our country to continue to be a leader as well as a partner in the efforts now underway.

The Human Genome Project is about ethical, legal, and social implications.

In fiscal year 1990, the National Center for Human Genome Research expects to spend approximately $1.7 million in support of a range of projects addressing the ethical, legal, and social implications of human genome research. This funding has allowed the Center's Ethical, Legal and Social Implications (ELSI) Program to accomplish four

important first-year goals: 1) fostering public education on genome research and its implications; 2) inaugurating open discussions of ELSI issues by the public, the scholarly community and policymakers; 3) initiating a program of research on priority areas of concern; and 4) facilitating the development of professional and social policy on key issues.

The ethical issues surrounding human genetics will not go away. Among many scientists there is acceptance of the belief that the "genie is already out of the bottle" and has been since long before the Genome Project was conceived. I believe that one of our highest priorities is to face these issues head-on, before they overtake us.

Conclusion

Mr. Chairman, the Human Genome Project was initiated in response to strong recommendations by the scientific community and after many years of debate. Although it was initially considered by many to be too complex and difficult, the faith of the project's initial proponents has been shown to be justified. The project appears to be more doable today than two years ago and progress continues apace. Many scientists who originally opposed the project have come to support it after examining the arguments in detail. The wise decision by Congress to invest in this project has born fruit. It has created a remarkable momentum in the scientific community and indeed in the whole world. It would be folly not to take advantage of this opportunity

to pursue a project that represents the cutting edge of science, an investment in long-term cost reduction, and extraordinary human promise.

Finally, may I say what a pleasure it has been to work with our sister agency, the Department of Energy. I particularly welcome the appointment of David Galas as Associate Director for Health and Environmental Research to carry on the important work begun by Charles DeLisi, who was the first to initiate a government-sponsored Human Genome Project. The two agencies work well together, both as collaborators and as friendly rivals. We keep each other on our toes. I look forward to a long and fruitful association.

Senator FORD. Thank you very much, Dr. Watson.

Dr. Galas, if you would proceed, then we will have some questions for both of the witnesses.

STATEMENT OF DR. DAVID J. GALAS, ASSOCIATE DIRECTOR, OFFICE OF HEALTH AND ENVIRONMENTAL RESEARCH, OFFICE OF ENERGY RESEARCH, DEPARTMENT OF ENERGY

Dr. GALAS. I am also pleased to be here with you today to discuss the role of the Department of Energy in the national effort to map and sequence the human genome.

I will present here a brief form of prepared statement. I will touch on the highlights of the prepared statement that I have submitted to you for the record.

Senator FORD. Fine. Your total statement will be included in the record, and we appreciate your highlighting.

Dr. GALAS. First of all, let me say that I concur with everything that Dr. Watson has said and would like to emphasize that there has been a spirit of——

Senator FORD. Would you pull your mike up just a little closer? We are trying to be frugal. We do not have the best PA system in the world.

Senator DOMENICI. You need new technology.

Senator FORD. We have the technology, we just do not have the money.

Dr. GALAS. Is that better?

Senator FORD. Yes.

Dr. GALAS. I concur with Dr. Watson, and that this program is certainly a very highly collaborative one between DOE and NIH and needs to be.

First, I will provide you with some background here on DOE's mission and interest in this area, and outline very, very briefly the thinking and events that led DOE to propose the original initiative.

In summary, in this initiative it was proposed that DOE develop the technologies resources and tools that will allow the scientific community, including DOE and NIH, to decipher the entire human genetic content at the molecular level. Now, the points I would like to touch on here are, first of all, how we have set up the initial phases of the program, some of the accomplishments to date, the mechanisms that are in place for coordination of NIH's and DOE's programs, something about the uses of the technology and resources that will develop from this program, and also something about the involvement of both programs in the ethical, legal and social issues.

First of all, let me say that this program will provide, among other benefits, quite a new approach to the traditional DOE mission, which is to understand the long-term health implications of energy technologies. The Department has long had research programs that are aimed at understanding the genetic and biochemical basis of health effects. The human genome research that the Department of Energy is involved has two general rationales.

Now the first of these is that it is a logical outgrowth of the past and ongoing DOE research in basic and applied genetics and molecular biology. And, secondly, that it continues DOE's past role in

the creation of new research technologies and resources for biomedical science. Both of these build, particularly, on the strong multidisciplinary national laboratory system that DOE has.

The scientific basis for the health and environmental concerns, I must emphasize, really must be understood before major energy policy questions that confront the Department and the Nation can be resolved. So this is another aspect or another facet of the importance of the genome project that has not been touched on by Dr. Watson's comments.

The primary scientific and health-related questions that the Department faces center on the long-term effects of low levels of radiation and energy-related chemicals. And seeking answers to these questions, fundamental biological questions I should say, constitutes a principal charge of the DOE Office of Energy Research.

Let me just point out that this charge has been repeated in several forms, all the way from the original Atomic Energy Act of 1946, the ERDA Act of 1974, to the Department of Energy Act of 1977. While the new knowledge that has been generated or will be generated by the human genome effort will certainly elucidate fundamental mechanisms, we need to understand these health effects. The impact, as indicated by Dr. Watson, will be much broader and much more significant to biology and to medicine in general.

The human genome project is expected to contribute, eventually, so much new knowledge to the scientific understanding for the functioning of living cells that it is certain to transform the science of biology, as was indicated in a couple of the letters you read, Senator. It will contribute to answering innumerable important biological questions, particularly concerning humans.

I think it is fair to say that all areas of genetics and molecular cell biology, and their applications to biotechnology will be changed by what is learned in the course of this project. So in effect, the research funds that are spent on other areas of molecular biology and cell biology will be made all the more effective and important in their results by the results of this particular project.

If I may, I would like to cite one particular example that is relevant to DOE; and that is the recent identification, cloning and characterization of four different human genes that determine the ability of human cells to repair damage to DNA. Each of these genes provides the coding information for an enzyme that acts within the cell on damaged DNA. This research, which is being done at the Oak Ridge Lawrence Livermore, and Los Alamos National Laboratories, will enable us to understand some of the biochemical mechanisms that are constantly acting in all of our cells to repair DNA damage.

Although this particular example is especially significant to DOE goals and not entirely the product of the project itself, it is the kind of advance that we expect to result from the project as it unfolds.

Let me turn for a moment to some of the technologies that are being developed in the human genome project. They are very likely to have significant applications, as Dr. Watson also said, in the private sector, as was the case with DOE-funded research in nuclear medicine. From what we know today, in fact, and in concurrence with another letter that you read, I believe that the technologies

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developed during the genome initiative will probably have even more impact in the private sector. I think that is without doubt true, since the fundamental basis of biotechnology is manipulating DNA. And that is precisely the sort of technologies that are being developed here.

A major thrust of DOE's biological research has been the evaluation of the genetic impact of radiation and energy-related chemicals. The Department has funded the development of a large proportion of all biological tests used to detect mutation. In fact, in studies to date, the available methods have provided no evidence for the induction by chemicals or by radiation, for the induction of heritable mutations in the DNA of the human genome.

There may be subtle infrequent changes, however, that have not yet been identified. These subtle changes may, indeed, have significant consequences for human health, and thus a major emphasis of DOE biological research has been the development of improved test systems for detecting mutations.

It is clear that improved mutation detection methods would require much more efficient ways to characterize the molecular sequence of DNA and to compare the DNA of offspring with that of their parents. It was this need for vastly improved large-scale DNA sequence analysis and an appreciation of the many implications that this capability had to biology in general that led the Department to address this question.

A workshop held in Santa Fe in March of 1986 concluded that, with the advances that were achievable in the technologies, the mapping and sequencing of the human genome was feasible by the end of the century; and if anything, we now think that the conclusions there were, perhaps, even cautious, given what we have learned in the last four years.

On the basis of that report, DOE developed its initiative and I think Dr. Watson has summarized quite well the sort of objectives that both NIH and DOE have had. DOE has had a particular emphasis, I should add, on development of technology and on the development of computer resources that are necessary to organize, analyze, and make the acquired information available to the scientific community. It was only a second phase of the project that we conceived of as focusing on large-scale sequencing; and of course, that would be highly dependent on results of the first phase.

Let me turn for just a moment, now, to some of the more recent events in the genome project. Now, as has already been said, the human genome program in DOE is $26 million for fiscal year 1990 and $46 million in the President's budget request for 1991. Our project for the coming immediate years emphasizes the construction of physical maps of each of the 24 different chromosomes—once again in collaboration with the NIH program—the development of computational tools, and the development of innovative technologies.

We are in the very early stages of pilot sequencing projects that are designed to test methods and to work out problems while acquiring significant biological information. DOE's program is going to focus in these early stages on the actively expressed sequences, which are rich in biologically important information; and we are

also supporting activities on the ethical, legal, and social implications, which I will return to in a moment.

I should mention that education and training are also very important in the conception of our program, and we have created a new post-doctoral training program to support fellowships in all aspects of human genome research, which is just beginning.

I am pleased to report that progress is being made in all of these areas, and our national laboratory and university affiliated researchers are engaged in constructing physical maps now of eight of the 24 different human chromosomes.

Several different mapping strategies are currently making major contributions to these efforts, and three of the chromosome maps are well advanced and will soon be in the final stages of completion.

Advances are also being made in the development of innovative DNA sequencing approaches. These include some of the more conservative approaches evolving from the automation and development of proven capabilities, as well as some rather high risk projects that could provide dramatic increases in efficiencies and cost effectiveness if they pan out. So we have a balance of developing present technologies to try to push them and automate them, and to explore entirely radical new technologies.

This spring the Department completed its program report entitled "Human Genome 1989-1990 Program Report", and I would like to, if I can, submit a copy for the Committee files.*

Senator DOMENICI. It will be accepted.

Dr. GALAS. It reports in much more detail on the current status and the future directions of the program.

Senator DOMENICI. Doctor, could I just interrupt for a minute, and both you and Dr. Watson—Dr. Watson, would you please get up closer to the mike. I am fearful that they did not hear your early testimony, because I did not catch it quick enough, but let me just ask you both a question.

Last year I was in Albuquerque, New Mexico at an annual fund raiser for cystic fibrosis. It was a gala celebration, because every year they had been raising money for research on cystic fibrosis. The chairman of the group and the parents, mother and father, and two cystic fibrosis children were there and, they were ecstatic; exhilarated. The genetic mapping and sequencing had occurred, and they had isolated the genetic problem for cystic fibrosis, and this was a big announcement. Now, I think some people are having a bit of difficulty understanding what we are talking about, but let me just ask you, why were they excited? Why were they thrilled that after all these years of research and what we understand—$120 million invested in genetic research—why were they excited, Dr. Watson?

Dr. WATSON. Well, they were excited because, through isolating the gene, researchers had found the defect in the protein which gives rise to the disease, and it is the hope that if we know what is going wrong——

*The report No. is DOE/ER-0446P dated March 1990, and has been retained in subcommittee files.

Senator DOMENICI. Let me just interrupt you. That isolation had occurred and there must then be some hope of what?

Dr. WATSON. Well, there is hope that we can go on and get a cure for the disease.

Senator DOMENICI. So, the scientists were handed—as a result of that connection—they were handed a tool for the possible cure or amelioration of symptoms of cystic fibrosis, is that essentially right?

Dr. WATSON. Yes.

Senator DOMENICI. Now, is it correct that the goal of this program, the mapping, and sequencing, if we can get the cost of sequencing down, is that we will hand similarly to the scientists of America and the world—bioscientists and others—that we will hand them similar information about scores of genetically related diseases—Down's Syndrome, and on and on? Is that why we are interested in this?

Dr. WATSON. Yes, and with our human genome program it will be much, much easier to find other genes. You will not have to spend $120 million. Because we currently know of at least 3000 genetic diseases—and I am sure many, many more are going to be discovered—it will be cost effective to get all these genetic markers so that when researchers begin looking for a disease, you do not have to essentially spend $100 million to come up with it.

If you say, "Well, what do we really want to get next?" I would like to get the markers so that we can find the gene for manic depressive disease. Now, that would be an equal occasion of rejoicing, I think, among all the families in which the disease is present—to actually know what has gone wrong within the body of the person who has this terrible affliction.

We want to get these genetic markers, and we want to make it easier for individual scientists to do this work. Some people say we are against little science. We think just the opposite. By providing these tools, we are going to make it possible for many more people, throughout our country and the world, to have a chance to actually locate these genes and to clone them.

Right now, there does not exist a set of easily available genetic markers which would allow someone, say in New Mexico, to do this work. They are highly localized. In some cases they still belong to a company. It is a mess, and the highest priority of our program is to make these markers available to everyone so that any genetic disease can really be mapped accurately.

Dr. GALAS. If I might add something to that, sir. It seems to be that we have reached a stage in the development of genetics and molecular biology where it is possible to stop looking at genes individually—where we can begin to systematically lay them all out. Just to give you an idea of the numbers involved, we know only about 3,000 human genes we know of, and there are, it is estimated, something like 100,000 genes. So if we do not begin systematically laying them out, then the fundamental understanding of the genetic functioning of the human cell, which is, at heart, what we need to know in order to approach each of these diseases individually, will not be there, and to do it systematically, now that we can, is the only approach that makes any sense.

Dr. WATSON. If I could go back to that. Some people say, well, why this targeted project, why the hurry? Why not just let the individual investigator (R01) grants come in, and not have this big program. I think if you are in a family with a serious genetic disease, you know, there are only a certain number of years you are going to live. You do not want that gene to be found 100 years after you are dead. So, if we can do this work over the next five years, I think we should do it. I have made a statement which some people have confused—I think we are doing the moral thing to try and get these genetic resources so we can get at these diseases.

Finding the real cause of many diseases is very hard, and we have only recently been successful with cancer because we could get so many of the so-called "cancer-causing" genes. There are many still remaining to be found, and our program is going to speed up the rate at which we can locate and identify these genes.

There is a gene on chromosome 3 which predisposes you to lung cancer. Well, if you can find it now, I would rather have it this year instead of 10 years from now. So I am in a hurry.

Senator DOMENICI. Dr. Watson, let me—and I apologize for interrupting you, Dr. Galas—let me just ask you: are we suggesting here that because of new technology, including computers and supercomputers and various new engineering techniques, that we are trying to accelerate the event in history, such as the cystic fibrosis celebration of last year, such that we may be celebrating these kinds of breakthroughs on a much larger scale and in much shorter time intervals for many of the dread diseases that people are currently researching and working on?

Dr. WATSON. Yes, I think so.

Senator DOMENICI. Do you have any doubt that this program will dramatically accelerate the tools and the knowledge for many of the diseases, such as this one, that are currently thought to be genetically related?

Dr. WATSON. I have no doubt whatsoever. I have never had one minute's thought that I am misleading people, or that I am misusing my time, or that federal money is being misused, and that this is some quixotic search into megalomania. It is not. It is just a very practical attempt to speed up the rate at which we can do high quality medical research. The total amount of money for the NIH genome program represents only about two percent of the NIH budget, and there are many medical problems where I think we are going to need these genetic tools, as well as the ingenuity which comes from individual research grants.

I am director of Cold Spring Harbor Laboratory, where people apply for individual investigator grants. I know the terrible situation they are in, and I think the reason that we have this crisis is not the human genome project, but the fact that biological research is now enormously effective. There are many more good ideas, many more good applications, and the money is not going up as fast as the quality of the science. That is our problem. It is not that the grants have gone from three to five years. We can do all these and we still have to recognize the fact that there will be a new Jonas Salk who is going to find out what causes alcoholism. We want to provide the resources so that these people, these individual people that we do not know about, can have grand enough ideas to

say, "I am going to finally get to the root of schizophrenia." It is a very hard problem, and I do not want to say that if we get our money for five years, we are going to come out and be able to announce to you that we have the cause for schizophrenia. I think we may get manic depressive disease, if we work real hard.

But, we are going to speed up the rate at which we can attack many essentially unsolvable—I mean problems which are too difficult to get at the real answer without the genetic approach.

Senator DOMENICI. Can I ask just one further question, Dr. Watson. We will deal with the competition between this program and the regular grant program with some dollar numbers and figures when the time requires here. But you can rest assured that the numbers that I have do not indicate that there is any squeezing out of the grant program at NIH by this program. Nor has the dollar number for those programs been cut for the grant program. Quite to the contrary, they are dramatically increased, and we will go into that a bit.

There has just been a change at the request of the scientists in how the grants are handled. They were turned into longer period grants and involve more dollars, so that is just arithmetic. If you do that, the amount of money that you appropriate goes for less grants, but the dollar number is up dramatically.

Having said that, let me just ask you this question. There will be a contention that as you produce this mass of scientific information some of it will not be useful. It seems obvious to me that is true, but as an expert and the one who actually has his place in history because you were the one that discovered the DNA, would you address the issue that as we move through this in an effort to expedite the handing over to the scientists of the map, address the issue of yes, we will find information we do not need, and does that justify us not doing the program?

Dr. WATSON. Well, you know we have high resolution maps of the United States, and occasionally we define some minor mountain that no one has thought worthwhile going up. But we have also defined a lot of very good things, and if you did not have the maps altogether, where would we be?

There is a lot of individual investigator research which has no consequences whatsoever. It is not as if every investigator-initiated grant produces some diamond. Most of them do not. But that does not mean you should not do them, because you do not know where the diamonds are.

And there has been the complaint that we are going to sequence all this "junk". We are not going to sequence that "junk" right now. For one thing, we do not know where the "junk" is to start with. And there are complaints that we are lousy scientists. Well, I want to ask these people to point out which member of my advisory committee and which member of these peer review committees are lousy scientists. They all have marvelous track records and I am proud of the group.

We are not out to waste our time or to waste federal money, we are out to get disease. The function of the National Institutes of Health is the Nation's health, not the health of a scientist—if I can make that distinction. We want to spend scientific money the best

way possible, to get at disease. And I think I want to get at Alzheimer's.

Senator FORD. Excuse me.

Dr. Galas, were you about finished?

Dr. GALAS. I just want to touch on two more points, sir, very briefly. First of all I just want to mention that a large component of the research that is carried out in the DOE program is carried out at the Human Genome Centers at the National Laboratories. And those are in Berkeley, California, and in Los Alamos, New Mexico.

And I am pleased to report to you today that Secretary of Energy James Watkins has authorized me to announce that a third center has been named, effective today, at the Lawrence Livermore Laboratory. And in the later panel, I believe that the now three center directors will testify to you.

Let me just summarize at this point and say that what Dr. Watson just said I think about going after disease is an extremely important point. But it is actually a stronger point even than that, because I think that the genetically related diseases are not the only ones that will benefit from a project of this kind. I mean systematically going after the genes in the human genome is something that will enhance dramatically and systematically the understanding of the way the cell functions and may involve the cure of diseases that have genetic components but are not considered in our present parlance to be genetic diseases.

Let me just say that this initiative from the beginning was seen as a new undertaking in biology, a new way of approaching things, and in some sense, I think a maturing of part of the science of molecular biology and genetics. In my view, it is going to enrich and invigorate all of biology and we will probably look back upon it as one of the important watersheds in the development of the science.

With that, I think I will conclude my statement and simply say that we look forward to working and continuing in a collaborative way with NIH on this exciting and challenging program. And that concludes my statement. I would be happy to answer questions.

[The prepared statement of Dr. Galas follows:]

Statement of David J. Galas

Associate Director

Office of Health and Environmental Research

Office of Energy Research

Department of Energy

before the

United States Senate

Committee on Energy and Natural Resources

Subcommittee on Energy Research and Development

July 11, 1990

Mr. Chairman and Members of the Subcommittee:

I am pleased to be here with you today to discuss the role of the Department of Energy (DOE) in the national effort to map and sequence the human genome. DOE and the National Institutes of Health are engaged in the effort to accomplish a detailed analysis, at the molecular level, of the entire content of DNA in the human cell, which is called the genome. I will first provide some background on DOE's mission and interests in this area, and outline the thinking and events that led DOE to propose the original initiative. This initiative proposed that DOE develop the technologies, resources, and tools that will allow the scientific community, including DOE, to decipher the human genetic material at the molecular level. I will briefly discuss the following: how we have set up the initial phases of our program; some accomplishments to date; the mechanisms that are in place for coordination of effort with other U.S. agencies and international programs; the uses of the technology, resources, and data that will be created; and our involvement in addressing the ethical, legal, and social issues relating to the program.

THE DOE HUMAN GENOME PROGRAM BACKGROUND

This program will provide, among other benefits, a new approach to a traditional DOE mission, which is to understand the long-term health implications of energy technologies. The Department has long had research programs aimed at understanding the genetic and biochemical basis of health effects. The human genome research by the Department has two general rationales: first, it is a logical outgrowth of past and ongoing DOE research in basic and applied genetics and molecular biology, and second, it continues DOE's past role in the creation of new research technologies and resources for

biomedical science. Both of these build on the strong multidisciplinary capabilities of the Department and its national laboratory system. The scientific basis for health and environmental concerns must be understood before major energy policy questions that confront the Department and the Nation can be resolved. Such concerns may have a major, perhaps deciding, influence on the mix of energy technologies with which we move into the future. The primary health-related questions faced by the Department center on long-term effects of low levels of radiation and energy-related chemicals, and seeking answers to these fundamental biological questions constitutes a principal charge of the DOE Office of Energy Research.

In the past, a variety of approaches has been used to evaluate the effects of low levels of radiation and energy-related chemicals. Each of these approaches has its limitations. In the absence of data on their direct effects on human health, science must depend on extrapolations from cultured cell and animal models, and there are serious uncertainties in extending the results of such studies to human health effects.

While the new knowledge generated by the human genome effort will certainly elucidate the fundamental mechanisms we need to understand these health effects, the impact will be much broader and more significant. The human genome project is expected to contribute eventually so much new knowledge to the scientific understanding of the functioning of living cells that it is certain to transform the science of biology. It will contribute to the answering of innumerable important biological questions, particularly concerning humans. It is fair to say that all areas of genetics and molecular cell biology, and their applications to biotechnology will be changed by what

is learned in the course of this project. One example, particularly relevant to DOE, is the recent identification, cloning and characterization of four different human genes that determine the ability of human cells to repair damage to DNA. Each of these genes provides the coding information for an enzyme that acts within the cell on damaged DNA. This research, which is being done at the Oak Ridge, Lawrence Livermore and Los Alamos National Laboratories, will enable us to understand some of the biochemical mechanisms that are constantly acting to repair damage to the DNA of the human genome. Although this example is particularly significant to DOE goals, and not entirely the product of the project itself, it is the kind of advance that can be expected as the project unfolds.

The technologies that are being developed in the human genome project are very likely to have significant application in the private sector, as was the case with DOE-funded research in nuclear medicine. It is estimated that millions of procedures based on nuclear medicine are performed annually in the U.S., and nuclear medicine has spawned industries operating at hundreds of millions of dollars per year. From what we know today, I believe that the technologies developed during the genome initiative will probably have even more impact in the private sector. The new technologies will find broad application in nearly all areas of biotechnology, not just human biology and medicine, but in every area which will benefit from more effective and efficient methods of manipulating and analyzing DNA.

Research that is now a direct part of the current human genome initiative has been underway since 1983 when the Department initiated the National Laboratory Gene Library Project. The purpose of this DOE project was to separate human

chromosomes and prepare cloned DNA fragments from each type of chromosome for the research use of the scientific community. The collection of stored DNA fragments from each chromosome is called a library. The project uses the unique strengths of the Los Alamos and Lawrence Livermore National Laboratories in the area of chromosome separation by using a technique called automated fluorescent flow cytometry, a Los Alamos invention. The library of cloned DNA fragments from each chromosome is a valuable research resource. These 24 libraries of clones, which are particularly important for our work, are also made available to the world scientific community.

A major thrust of DOE biological research has been the evaluation of the genetic impact of radiation and energy-related chemicals. To cite one example, at the Oak Ridge National Laboratory, DOE funds one of the world's largest centers for the study of mouse genetics which includes research on the genetic effects of chemicals and radiation. In the past, the Department has funded the development of a large proportion of all the biological tests used to detect mutations. DOE and its predecessor agencies have funded the largest genetic study of a human population ever undertaken, the attempt to detect heritable mutations in the survivors of the atomic bombings in Japan. Efforts that have been ongoing since 1946 have found no more mutations in the offspring of the survivors of those bombings than were found in the unexposed population. In fact, in these and other studies to date, the available methods have provided no evidence for the induction (by chemicals or by radiation) of heritable mutations in humans. There may be subtle, infrequent changes, however, that have not yet been identified. These subtle changes may have significant consequences for human health and, thus, a major emphasis of

DOE biological research has been the development of improved mutation test systems.

A 1986 report from the Office of Technology Assessment (OTA), "Technologies for Detecting Heritable Mutations in Human Beings," discussed the needs for improved methods for mutation detection. The report surveyed available methods and considered recent advances in molecular biology which could lead to techniques for identifying mutations. The report noted that "of the several funding agencies, DOE has taken the lead in funding much of the research on new methods for mutation detection described in this report, and researchers at some of DOE's national laboratories are among the leaders in the research."

It was clear that improved mutation detection methods would require much more efficient ways to characterize the molecular structure of DNA and to compare the DNA of offspring with that of their parents. It was a need for vastly improved large-scale DNA analysis and an appreciation of the many implications of such a capability that led the Department to organize a workshop of eminent scientists. That workshop, held in Santa Fe in March 1986, concluded that, with achievable advances in technologies, the mapping and sequencing of the human genome was feasible by the end of the century. The workshop report concluded that the effort would require a central coordinating body and multi-institutional support and cooperation, as well as a multinational constituency.

On the basis of this report, DOE developed a major new initiative on mapping and sequencing the human genome. The initiative was originally conceived as having two phases. The first phase would have three goals: (1) the production of a physical map of the human genome in the form of ordered, cloned DNA fragments; (2) the development of high-speed, fully automated methods for sequencing DNA; and (3) the development of the computer resources necessary to organize, analyze, and make available the acquired information. The second phase would focus on large-scale sequencing and would be heavily dependent on the results of the first phase.

The program was envisioned as a coordinated, multidisciplinary effort that would first create the technologies, tools, and resources to allow rapid, cost-efficient studies of human biology through genome analysis. In May 1986, the DOE Health and Environmental Research Advisory Committee (HERAC) was charged with providing advice on the scientific, organizational, and administrative strategies for achieving the goals of the initiative. The HERAC Report on the Human Genome Initiative was delivered to DOE in April 1987. This initiative formally began in FY 1988, at a level of approximately $11 million.

It is gratifying to note that the approach outlined in the DOE initiative and the HERAC Report is consistent in its scientific strategy with the later report released in 1988 by the National Research Council, "Mapping and Sequencing the Human Genome." It is also consistent with the 1988 report prepared by the Office of Technology Assessment, "Mapping Our Genes, The Genome Project: How Big, How Fast?"

RECENT EVENTS

The budget for the DOE Human Genome Program is $26 million in FY 1990, and is nearly $46 million in the President's FY 1991 budget request. It emphasizes the construction of physical maps of each of the 24 different human chromosomes; development of the computational tools needed to enter, retrieve, and analyze mapping and sequencing data in large databases; and development of new, innovative technologies for mapping and sequencing, and for rapid, cost-effective analysis of DNA sequences. We are in the very early stages of pilot sequencing projects designed to test methods and work out problems, while acquiring significant biological information. We are also supporting activities addressing the ethical, legal, and social implications of the potential uses of genetic information resulting from this program. A new postdoctoral training program to support fellowships in all aspects of human genome research is getting underway.

I am pleased to report that progress is being made in all these areas of the DOE program. Our national laboratory and university-affiliated researchers are engaged in constructing physical maps of 8 of the 24 different human chromosomes. Several different mapping strategies are currently making major contributions to these efforts. Three of the chromosome maps are well advanced, and will soon be in the final stages of completion. Computer scientists at national laboratories and universities are making available to the scientific community new computer programs for handling data, which facilitate the retrieval and analysis of mapping and sequencing data from large databanks. Advances are also being made in the development of innovative DNA sequencing approaches. These include some of the more

conservative approaches evolving from proven capabilities as well as some high risk projects that could provide dramatic increases in efficiencies and cost-effectiveness. Last spring DOE published the first issue of a newsletter which reports on genome research and related activities and serves to communicate with the broad scientific community and other interested groups. This spring, the Department completed its program report entitled "Human Genome: 1989-90 Program Report." It reports on the current status and future directions of the program in detail. Also this spring, the National Institutes of Health (NIH) genome program joined us in sponsoring and contributing to the bimonthly newsletter, which is currently distributed to over 3,400 addressees.

COORDINATION

DOE genome project activities are coordinated with the NIH effort at the National Center for Human Genome Research under the auspices of the Memorandum of Understanding signed in the fall of 1988. A joint subcommittee of the DOE HERAC and the NIH Human Genome Advisory Committee has been established to assist the two agencies with program oversight and coordination. This subcommittee has organized four joint working groups made up of technical experts which report to it on mapping, sequencing, informatics, and ethical, legal, and social issues. Earlier this year the agencies completed the five-year plan for the Nation's human genome project, "Understanding Our Genetic Inheritance, The U.S. Human Genome Project: The First Five Years FY 1991-1995." This kind of cooperation is necessary to maximize the productivity of the national program and to avoid unnecessary duplication of work in the scientific community.

Together with the National Center for Human Genome Research at NIH, the Department supports and participates in a joint working group on ethical, legal, and social issues associated with this area of research. The problems in society that may arise from the availability of genetic information of unprecedented detail should be anticipated and considered carefully before that information becomes available. Both DOE and NIH consider it important that we take measures now to examine possible problems and to help educate the public. We are earmarking 3 percent of the DOE human genome operating expense budget for each fiscal year to support the study of problems in this area. It is likely that a majority of these funds will support educational activities designed to foster understanding by society of the basic elements of genetic inheritance.

We also interact with genome programs that are developing in other countries. For example, U. S. scientists, including several from the DOE program, are taking active leadership roles in the international Human Genome Organization (HUGO). HUGO was initiated in 1988 to assist funding agencies and scientific communities with the coordination of research and related activities on an international level. We encourage the role of HUGO as the principal international coordinating group for the human genome project.

TECHNOLOGY TRANSFER

The Department of Energy is aggressively pursuing the involvement of American industry in the genome program. Interactions that are developing between industry and the national laboratories, where the major part of the DOE effort is centered, are expected to facilitate the ultimate commercialization of

innovative technologies. An example of this is the formal cooperative effort between industry and the Los Alamos National Laboratory Human Genome Center for shared funding and staffing of research related to instrumentation development and computational sciences. A second is the modification of computer software developed at the Lawrence Livermore National Laboratory by a biotechnology firm for direct use with commercial, advanced biotechnology equipment.

In summary, Mr. Chairman, this initiative from the beginning was seen as a new undertaking in biology as well as a new departure for DOE. It will change the sciences of biology and genetics substantially and contribute strongly to DOE's several interests. In my view, it will enrich and invigorate the biological sciences. As the HERAC Report states, "This special focus on technological development is distinct from the current national effort in human biology and genetics and requires a new initiative." The reports of the National Research Council and OTA similarly recognized these new technological and scientific horizons. Each of these reports emphasized the need for new technological tools and noted that creation of these tools will require a broad interdisciplinary research effort, one that brings together expertise from a variety of fields, such as engineering, electronics, optics, computing, physics, and chemistry, as well as biology. DOE brings considerable and unique experience to the task of organizing such diverse disciplines to focus on a coordinated, multidisciplinary effort to develop complex new technology. Major advances are required in several areas. We need to develop automated and more effective techniques for handling, mapping, and sequencing DNA, and we need new approaches in computer analysis for deciphering the biological

messages encoded in the DNA of the genome. DOE has unparalleled resources and expertise to apply to this effort. We look forward to continuing our work on this important and challenging project in coordination with NIH and other involved federal and private organizations.

This concludes my prepared statement. I will be happy to answer questions.

Senator FORD. Thank you very much, Dr. Galas. I have two or three questions. And Senator Domenici may have some more.

The questions I have are in some respect related to what Senator Domenici asked earlier. And I would ask it in a little bit different manner, maybe a country boy's questioning.

Dr. Watson, your critics have questioned the rationale of this project, and you are well aware of that, to determine the entire structure of the human genome. And I have been led to believe that there could be as much as 97 percent of the genome that appears to have no function. And as you related to it a while ago, it was called "junk" by some researchers.

And then you said a few moments ago that the $3 billion that we have been referring to may be an uncertain number as it relates to the cost. And so, therefore, are taxpayers being asked to spend $3 billion to study "junk"? If not, how will this money be more carefully targeted?

You have touched on that with Senator Domenici and I would like to get a more definitive answer so that we can pursue this.

Dr. WATSON. I will start off by saying that at least the first third of the genome program is going to be focused totally on mapping. So if you figure $1 billion for mapping, and we know it is going to work, we are absolutely certain it will be cost effective. And we should get it done as fast as possible because there are all of these genetic diseases out there.

As to the sequencing, we are going to try and get the cost down. We have set 50 cents a base pair as our goal, which would be a total of $1.5 billion for sequencing. And I think we must wait to see how things progress. If you take the material which is known to be in genes, there are regions which you could say are functional and those which are apparently nonfunctional. Those regions that code for amino acids, which are functional, might only be 5 percent of our DNA.

On the other hand, next to it are regions which we know control the functioning of these other regions. So, what fraction of the genome is not functional we cannot now say. Five years from now it will be a question of how fast we want to go ahead. My own guess is that we will develop tools that, when we sequence through this "junk" DNA, will be able to distinguish the "junk" from the not-"junk" and put the whole thing together.

One part of our program which I failed to mention earlier is that the first sequencing we want to do is of model organisms—bacteria and yeast—where we know there is no "junk". We want to find the basic structure of all the proteins because we know these proteins are very similar in humans and in yeast. You can interchange them. So, if we get the protein structures in yeast, which is a relatively inexpensive job, we will have, I think, a rather powerful tool for going on to humans.

So I would like the freedom to appear before you five years from now to talk to you about whether you want to appropriate this money.

Senator FORD. Why do not we just say that if you and I are both here we will have you in. Your chances of being here may be better than mine.

Dr. WATSON. I think you look pretty healthy, sir.

Senator FORD. I am not talking about health. [Laughter.]

But I am not going to vote to raise taxes. [Laughter.]

Dr. Watson, some of our witnesses today, and I have had an opportunity to read their statements last evening, will testify that in time of very tight budgets, and we are moving faster into that area than we would like to admit, that the available new federal money should be going to individual investigators studying specific health problems, instead of the human genome project, which is siphoning off the available money for the so-called big research centers dedicated to an abstract chemical analysis of the DNA molecule.

Dr. WATSON. I believe they cannot read. We are not going to do that. We are going to complete these maps. We are going to get the pieces of DNA. We are not out to waste the Nation's money. And as I tried to state before, when you have a certain amount of money, you have to decide on the best way to go after your medical problem.

I think the best way is to use genetics whenever possible. It has proven the way to go in the past. I think it is going to be the way in the future. And if I had to make a choice between getting this genetic map and funding some more individual investigator grants (R01s) I would get the genetic map.

Now, I would like to have both the R0-1s and the genetic map. And I believe that science is now so exciting that everyone should consider whether more money should go towards science. But, given the limited pie, I would have to say we have got to get these maps.

You can spend money from here to eternity on some forms of mental disease and you are not going to get anywhere. We throw away a lot of money because we are human beings and we want to do something. But I think we want to try and do the most effective thing. You have to make choices in this world. I think we are making the right choice in supporting the human genome project.

Senator FORD. Dr. Galas, DOE originally conceived of a human genome project—I believe it was 1986, 1987. And today's genome project is different from the one that DOE started out to establish. Could you explain the changes and why they are good changes, if they are?

Dr. GALAS. Well, indeed, I think they are, Senator. I think there are several major differences. One is the obvious one, that now, in the present project, we are working very closely with NIH. And we have done that in such a way that there is very little, if any, redundancy and we have helped each other enormously. In maybe a rare occasion, I do not know, the two agencies have actually learned a lot from each other.

Another major difference between the early days and now is, I believe, what was originally proposed was that because we could now sequence the human genome, let us go ahead. It has been recognized since then that mapping is the major focus for the initial part of the project. It has become not so much a huge effort to go after randomly, or systematically, all the DNA sequence, but rather to do it in a very stepped, very logical way, to focus on what can be done first, and to focus on the information which will have the maximum biological impact on the rest of science.

Another thing that we have learned in the ensuing years is that the technological developments that we could not conceive of then have now in many cases come—much closer to reality. The rate at which we can map things now is something that we would not have probably predicted back in 1986. And so we are much farther along, in some sense, than we might have thought we would be in terms of the mapping.

The three mapping projects that are going on at the Human Genome Centers at the National Labs, for example—I would say—it is rough; it is difficult to get a rough estimate of quantitatively how far along you are in a map; but there may be something like 50 percent complete. And maybe that last half is going to be very difficult. But all of a sudden several new techniques have come along that look very promising, and it looks like we will be moving into the final stages of the maps on these first chromosomes very soon.

Senator FORD. Dr. Galas, Dr. Watson was favorably inclined in the association that NIH and DOE have. Is the role that you now have, is that the proper role for NIH and DOE in the human genome project?

Dr. GALAS. I believe it is, Senator. They are very complementary in the way in which we can go about it, and the resources that we have to focus on this project. Using the multidisciplinary National Laboratories has been a great advantage in the initial stages of the project: to attempt to bring together the capabilities in engineering, physics, computer science and so forth, to attempt to focus on some of the technological developments that are required is something that NIH has had much less experience than DOE. And I think it has worked out to be quite a favorable partnership. NIH has contributed a great deal to the scientific enrichment of the projects at the National Laboratories as well.

Senator FORD. Thank you very much.

Senator Domenici, do you have any other questions?

Senator DOMENICI. I have a few.

Dr. Watson, let me first say, I think because this Subcommittee, a few years ago, began to push the genome project within the Department of Energy, that the National Institutes of Health came alive. And now we have a very exciting partnership. But I also want to say to you personally that that event caused the National Institutes of Health to go off to Cold Spring Harbor and to ask you, the Nobel Prize winner for finding of the structure of DNA, to come here and head this program. And I want to commend the NIH and congratulate you for leaving your research and teaching to come and head this program.

Now having said that, I would like to ask you: Doctor, how confident are you that some of the very significant diseases that plague mankind—let me give you a couple: schizophrenia, manic depression; let us just take those two—how confident are you that this program will accelerate findings leading to treatment and/or cure of those kind of diseases?

Dr. WATSON. I am very confident that we can find the defect in our brains which leads either to the manic depressive condition or to schizophrenia. We know both have genetic components. The inheritance of manic depressive disease is clear. It moves through

families with an awful regularity. Schizophrenia is harder to diagnose but if you look at identical twins, you can see there is definitely a genetic component.

There was a paper published last year which tried to associate schizophrenia in certain families to chromosome 5, but the research has not been repeated; Many people are now trying to put together the pedigrees, and I am confident that we will certainly succeed with manic depressive disease, and we will work very hard on schizophrenia.

It is when you have a condition as a result of several different genes that it is a harder problem. You can give reasons for saying it is too difficult, but most of the things that science has accomplished there were people who said it was too difficult.

If I were young, I would not think I was wasting time up going after the genetics of manic depressive disease. I would think of it as a good way to make my career. I think you are going to succeed, if you use your brains and you get the resources which our program will put together.

Dr. GALAS. May I add something to that, Senator?

Senator DOMENICI. Sure.

Dr. GALAS. Those two diseases that you describe, most people think are caused by, or at least are contributed to, by many genes, or at least several genes. And so that being the case, it is only this sort of systematic approach to laying out the mapping and location identification of genes that has much chance of success.

Without this kind of a project, those diseases that involve lots of genes, which are not the ones that have been studied to date, primarily because of that reason, would not really be accessible. So it is about time that we approach it.

Dr. WATSON. For the whole mental health problem I think we need a very strong human genome program, which will give to the psychiatrists, and to the whole community, the set of genetic markers. They can then go out into their communities, get the pedigrees, and try to make sense of the data.

Our Center intends to work very closely with the National Institute of Mental Health. And if we cannot give you something in five years that is bad.

Senator DOMENICI. Doctor, let us talk a minute, either of the Doctors, about what is going on in the world; if the United States were not to proceed with this genome project—at least, the first phase of mapping? Could you briefly tell the Committee: is Japan interested in proceeding with some kind of genetic mapping?

Dr. WATSON. They are doing a little. Right now it is our impression they are more interested in instrumentation development than in mapping per se, but we cannot be sure of that. The general problem my Japanese colleagues constantly complain about, is that the support of pure science in Japan is still relatively low compared to the United States. They do not have a strong human genetics intellectual life like you find in the United States and throughout Europe.

Mapping, if the United States was not doing it, would simply be going ahead in the U.K., France, Scandinavia and Italy. Right now, we are seeing an acceleration of their efforts because of the American program.

I think they may be a couple of years behind the U.S. I had a letter from one of the best scientists in Sweden saying they and the Russians were thinking of a real program on chromosome 3. I was very pleased. There is a very important anticancer gene on chromosome 3 that they want to work on and it is too interesting and too important not to do.

Dr. GALAS. Sir, the Japanese program, as far as I know, is something like $7 million in this year, and scattered throughout four different ministries. And I concur with what Dr. Watson said about it, but I should add that if we were not doing this, eventually, I do not know how many years it would take, they are going to be a major force in this. It is just that we are ahead now.

Senator DOMENICI. Last question. Relationship between DOE and NIH, DOE answered, but would you answer? Is that relationship working well now, Dr. Watson?

Dr. WATSON. I do not think it could be better. There was a lot of skepticism that we were going to be fighting. We have not had a fight at all. Because there is so much to do, and we want to get it done, and if we work together we will get it done faster. We are all personal friends. It is not as if you have two groups that dislike each other. We are friends, we have a common cause, and we are going to work together.

Our major problem will be interacting with the rest of the world. But as far as the United States effort, it is very well coordinated.

Senator DOMENICI. If this is, and I am not at all sure it is, but if this is big science versus little science, frequently one of the objections to big science is cost overruns. Could you tell us the cost estimates in this program? Are we on the mark from what you can tell? Or are there going to be cost overruns in the first phase?

Dr. WATSON. In the first phase there will not be cost overruns. We will get the job done. We just have to. The key to getting the job done is combining the talents of researchers from several disciplines toward accomplishing one of the major goals of the human genome program and putting them together in teams. These are our so-called "centers". These are not giant places of 500 people. The centers we are proposing under our program are a critical mass of 20 to 30 people. They are absolutely essential to getting the job done.

We are not going to stop R01s. In fact, within these centers there will be researchers with R01 grants. So it is really a way of letting small scientists work together. Centers are absolutely essential. They are a sign of success, not of failure. If we are going to get the mapping job done over the next five years, we also need the DOE centers. I would hope that DOE might add a few more within their National Labs so that we can get the chromosomes done—just get them all done.

Senator DOMENICI. Thank you. Thank you, Mr. Chairman.

Senator FORD. Thank you, Senator. I have no further questions. There may be some questions from other members who are not able to be present today, and we will submit those to you in writing and hope that you will respond in a timely fashion.

We are very pleased that both of you came today and testified. We are pleased that you are friends. My explanation from my dad to me when he and mother seemed to be arguing was that they

were just discussing the situation. And so if it appears to be an argument, you all are just discussing the situation. We accept that.

Thank you both. We look forward to seeing you at least five years from now.

Dr. GALAS. Thank you, Senator.

Senator FORD. The next panel will be Dr. Charles Cantor, Director, Human Genome Center, University of California at Berkeley, the Lawrence Berkeley Laboratory; Dr. Robert Moyzis, Director, Human Genome Center at Los Alamos National Laboratory; and Dr. Anthony Carrano, Director, Human Genome Center, Lawrence Livermore Laboratory.

Dr. Cantor, we will ask you to go first. We are being pushed a little bit on time. We spent a little bit more time on the last panel than we should have. I do not want to jeopardize anybody's statement, but if you would submit your statement for the record and highlight it, it would give us an opportunity then to have some dialogue rather than our time squeeze.

So, Dr. Cantor, under those circumstances, we will be glad to put your statement in the record and hope that you would highlight your statement.

STATEMENT OF DR. CHARLES R. CANTOR, DIRECTOR, HUMAN GENOME CENTER, LAWRENCE BERKELEY LABORATORY

Dr. CANTOR. I am going to abbreviate my statement, Senator, as requested. I will try to avoid duplicating things we have already covered.

I want to first express my appreciation for the opportunity to address this Committee, which has been so supportive of the human genome project. I am going to limit my comments to those areas of the human genome project that go beyond the discovery of disease genes because we have talked about that plenty already. But there are other implications. I just feel I have to make one comment about "junk" and disease.

We have at least one well-known case, phalasemia, where disease is caused by DNA defects in regions which are usually termed "junk". And so we have to be very careful about this distinction that "junk" can lead to disease.

What I want to do in this brief presentation is highlight the implications of the genome project for biomedical research in general and for American industry.

Today we already have a host of powerful tools and instruments for DNA mapping and sequencing. And what is striking is that none of these tools existed eight years ago. Many U.S. companies like Applied Biosystems, Cetus, and Perkin-Elmer are now thriving on the advances in technology over the past few years.

But driven by the needs of the human genome project in the next decade, there are going to be really major further advances in biological instrumentation. I think these are likely to be revolutionary. The enormous size of the human genome means that today's methods have to be replaced by ones that are 10 to 100 times more powerful. And I predict that eventually most of the genome will be sequenced and much of it mapped by methods that

do not exist today. These methods are likely to spawn a wide range of new commercial instruments and applications.

Now the key factor is that the new methods are applicable to all of biological research and not just to the human genome. In any organism, it is far more efficient to find all the genes simultaneously and systematically rather than hunt for them one at a time. So as this new technology reduces the cost of mapping and sequencing, what is going to happen is parallel genome programs will be established for a wide range of plants and animals of commercial importance.

Many of these projects are likely to be centered in the private sector. I think they will have broad impact far beyond medicine.

Two key areas where human genome project technology is certain to change the way in which a broad aspect of science is done are robotics and information science. At Berkeley we are collaborating with Hewlett-Packard to eliminate one of the most boring and labor-intensive steps in the project and in many other biotechnology endeavors.

When bacteria or yeast are grown in the laboratory, they occur at random locations which we call clones. And this randomness is a severe limitation, because in some cases one needs to systematically sample and analyze 50 to 100,000 such clones to find ones of particular interest. We now have been able to program a robot to do this automatically and take these random clones and transfer them into a regular pattern so that they can then be handled by automatic machinery. The important thing is that such automation is error-free, and you always have a precise record of what was done.

Robotics applications are not limited to clones. They can also be used on single cells or even single molecules. A brand new example of this is laser tweezers technology, which is currently being commercialized by Cell Robotics, a new biotechnology company in Los Alamos.

But perhaps the most impressive thing about the human genome project is the massive amounts of complex data that must be handled. If we actually had the human genome sequence today we would be deluged. It would be very difficult to handle it.

Besides the 3 billion base pairs of DNA sequences, we need to manage data from experiments and samples that lead to these sequences. It is no surprise that companies like IBM and Cray are eager to understand the current needs of the genome project and its future needs.

Today much of the data is in the form of images, photographs, x-ray films, pictures and microscopes. Currently images are handled manually using hard copy, but this cannot continue when you have thousands or tens of thousands of images. At Berkeley we have developed computer methods to handle all of these images by building on a prototype that the University of California put together to handle their collection of archeology photographs. In this way, by taking a method that already existed, we were able to save considerable cost. I expect enormous increases in our power to work with images over the next few years.

At Berkeley our principal target within the genome is the smallest human chromosome, chromosome 21. It is particularly interesting to us because it is the site of genes that affect mental health,

including Alzheimer's disease and Down's syndrome. We have cut this chromosome into 60 pieces and have now placed almost all of these in order. The next stage is to subdivide these pieces into smaller fragments that we can propagate indefinitely and, most importantly, that we can distribute to others, which is ultimately necessary to facilitate sequencing the DNA and finding the genes on it.

Now the human genome project is a bit unusual in that it is geographically distributed. But it is functioning efficiently by cooperation between different laboratories. For example, some of the computer capabilities that we have developed at Berkeley are being sent to the National Library of Medicine so that they do not have to duplicate our efforts. This will help keep the cost of the project in bounds.

Coordination among various activities is particularly effective within the DOE human genome program because so much of that program is centered at the moment in just three locations—three national laboratories. This makes it much easier to know what is going on.

For example, both Dr. Moyzis and our group are interested in the ends of chromosomes. But we keep in contact so we do not duplicate each other's efforts. And Dr. Carrano, whose laboratory is located relatively near to mine at Berkeley, has been enormously helpful in the last few months in transferring certain new technical developments to us. These types of interactions are likely to continue. And again, I think they will really help keep the project on budget.

I hope in this brief presentation I have given you some feeling for the excitement and importance that pervades this project. I think it will surely be looked back on as one of mankind's greatest scientific endeavors.

Thank you.

[The prepared statement of Dr. Cantor follows:]

Testimony of Dr. Charles R. Cantor before the Senate Energy Research and Development Subcommittee, July 11, 1990.

I am grateful for the opportunity to address this committee. I appreciate the strong support it has provided for the initial stages of the Human Genome Project. My name is Charles R. Cantor; I am currently the director of the Human Genome Center at the Lawrence Berkeley Laboratory and Professor of Molecular Biology at the University of California at Berkeley. I also chair the committee of scientists that coordinates all of the DOE's Human Genome Research programs, and I serve the international human genome organization, HUGO, as vice president for the Americas.

In my limited time I will comment briefly on a few major points. I will describe some of the work ongoing at Lawrence Berkeley Laboratory and related work elsewhere. I want to highlight its long term implications both for biomedical research and for American industry. To put this in perspective, what is unique about the Human Genome Project is not its size but its structure. We could begin to sequence all 3 billion base pairs of human DNA with existing technology, but the cost in time and money would be high, and, if we had to rely solely on today's technology, we would be overwhelmed by the resulting information. We need to cut the costs, and develop the tools to optimize our ability to use the results.

Roughly half of the funds in the Human Genome Project will be spent on the development of new methods. Today we already have a host of powerful tools and instruments for DNA sequencing and related activities. It is striking that none of these tools existed 8 years ago. Many U.S. companies such as Applied Biosystems, Cetus, and Perkin Elmer are now thriving on these advances. Driven by the needs of the Human Genome Project in the next 10 years, we will see further advances in biological instrumentation that can only be called revolutionary. The awesome size of the human genome means we have to supplant today's methods by ones 10 to 100 times more powerful. I predict that eventually most of the Genome will be sequenced by methods that do not exist today. These methods will spawn a wide range of new commercial instruments and applications.

The key implication of the new methods is that, together with the information derived from the human DNA sequence, they will be applicable to virtually all biological research. At present, an enormous amount of

effort is spent finding and sequencing individual genes (The Cystic Fibrosis Foundation has estimated that it cost $120 million to find the single gene that causes this disease). It is far more efficient to find many genes simultaneously and systematically. This is true for any organism, not just the human. As new technology reduces the cost of mapping and sequencing, parallel genome programs will be established for a wide range of plants and animals of commercial importance. Many of these projects are likely to be centered in the private sector. Thus the new technologies will have an impact far beyond medicine: they will also greatly enhance our ability to do agricultural research and development.

Two key areas where Human Genome Project technology is certain to have broad impact are robotics and information science. Much of biological research is tedious and repetitive. At Lawrence Berkeley Laboratory we are working in collaboration with Hewlett-Packard to eliminate one of the most boring and labor-intensive steps in the Human Genome Project and many other biotechnology endeavors. When bacteria or yeast are grown in the laboratory, they occur at random locations, which we call colonies. This randomness is a severe limitation because in some cases one needs to systematically sample and analyze 50 to 100,000 such colonies to find the ones of particular interest. We have now programmed a robot to help. Using powerful new imaging methods, we first find the location of the colonies and pass this information along to the robot. It directs a mechanical arm to pick up one colony at a time and replant it systematically in a regular pattern which can then be handled by automatic machinery. The robot cannot actually do this task faster than humans can; the important thing is that it will never get bored, never mix up two samples, and it will always maintain a precise record of what it did. The difference is like mechanized harvesting of an orderly array of nearly identical crops instead of picking crops by hand from a wild field. Robotics applications are not limited to colonies. They can also be used on single cells or even single molecules. An example is the laser tweezers technology currently being commericialized by Cell Robotics, a new biotechnology company in Los Alamos.

Perhaps the most impressive thing about the Human Genome Project is the massive amounts of data that must be handled. It is no surprise that companies like IBM and Cray are eager to understand the current and future needs of the project. Besides the 3 billion base pairs of DNA sequence, we need to manage all of the data from experiments and

samples that lead to this sequence. Today much of this data is in the form of images: photographs, x-ray films, micrographs. Much more effective ways are needed to archive, analyze, and distribute these images. Currently images are being handled manually using hard copies, but this cannot continue. At Lawrence Berkeley Laboratory we have developed computer methods to handle all of the images created in the Human Genome Project. Fortunately we were able to build on a prototype that had been created to handle the University of California at Berkeley's enormous collection of archeology photographs. Now we are in a position to compare genome images, enhance them, and in some cases analyze them automatically. I expect enormous increases in our power to work with images over the next few years. The need to store and process images is not unique to the Human Genome Project. Our whole society thrives on images and our ability to handle them automatically is very primitive. For example, how do you find a newspaper or magazine photograph if all you remember is a particular detail? Today we cannot do such a task. The same kind of problem exists in the Human Genome Project in a simplified form where we may actually be able to solve it. Success could pave the way for more general solutions which will eventually change how we interact with computers in our every day life.

At Lawrence Berkeley Laboratory, our principal target within the human genome today is chromosome 21. This is the smallest chromosome and thus potentially the easiest to work with. It is the site of genes that affect mental health including Alzheimer's disease and Down's syndrome. We have cut this chromosome into 60 big DNA fragments and have now placed most of these in order. The next stage is to subdivide these pieces into smaller fragments that we can propagate indefinitely and distribute to others. This is necessary to facilitate sequencing the DNA and finding the genes on it.

The Human Genome Project is geographically distributed, but it is functioning efficiently by cooperation between different laboratories. For example we are currently using the Hewlett-Packard robot to process samples provided by or needed by Lawrence Livermore National Laboratory. This summer we will transport our image database to the Eleanor Roosevelt Institute in Denver for use there on chromosomes 21 and 3. Other informatics capabilities that we have developed are being sent to the National Library of Medicine so they do not have to duplicate our efforts. All of this will help keep the cost of the project in bounds.

Coordination is particular effective within the DOE Human Genome effort because so much of it is centered in three national laboratories. This makes it easier to avoid unnecessary duplication and share new developments rapidly. For example, like Dr. Moyzis at Los Alamos National Laboratory, we are also interested in chromosome ends. Frequent communication between the laboratories has ensured that our separate efforts are different and mutually beneficial. As another example, Dr. Carrano and some of his Livermore staff have been extremely helpful to us in solving a number of experimental problems in the past few months alone. The DOE Human Genome Coordinating Committee is meeting regularly to insure that these interactions are frequent and productive.

I hope I have given you some feeling of the sense of excitement and importance that pervades the Human Genome Project. It is both a pleasure and a priviledge to be involved in a project that will surely be looked back on as one of mankind's greatest intellectual endeavors.

Senator FORD. Dr. Moyzis.

STATEMENT OF DR. ROBERT K. MOYZIS, DIRECTOR, CENTER FOR HUMAN GENOME STUDIES, LOS ALAMOS NATIONAL LABORATORY

Dr. MOYZIS. Likewise, I have a prepared statement but I will try to summarize.

Senator FORD. Your total statement will be in the record.

Dr. MOYZIS. Again, it is a real pleasure to be here, talking to you about what I think is one of the most exciting and challenging projects in the history of science. Most of my colleagues have already talked and many will talk yet today about their excitement about this particular project. What I would like to do today is just briefly share with you a few of the recent accomplishments at Los Alamos, and end with a statement again reiterating why I think it is absolutely essential that this project be pursued.

One of our first accomplishments in, really, the first year of funding of this project, was the identification and cloning of the human telomere. Now, it is a bit of jargon, but it really is just the ends of the chromosomes that are present in each one of your cells. The reason I am pointing this out is, I think the telomeres are a beautiful example of what critics would call junk. It is not a protein coating region. It does not do anything obvious if one just looks at this sequence.

In fact, it is probably one of the most critical sequences in the genome. Without this sequence, you would not be alive today, sitting here talking to me, nor I alive talking to you. It is a vitally important sequence. The impact on the human genome project of the identification of the sequence is really very easy to, I think, summarize. If you ever try to put together a jigsaw puzzle, what is the first thing you do? You try to get the ends.

Well, right now, human genetic maps are almost like 16th Century maps of the world. We have very detailed knowledge of some regions of the map, whereas other regions are really totally unknown. We do not even know where a continent ends, for example. Well, the isolation and identification of the sequence got the ends of the map. We now know the beginning and the end of the human genome map, and just like the jigsaw puzzle analogy, it is going to make it a lot easier to put the remaining pieces together.

A second accomplishment, and I think you will hear again from Dr. Carrano about this, is our excitement that the focused efforts at the labs, and particularly I will talk about the experience at Los Alamos, of actually producing a genetic map of an individual chromosome and a physical map of an individual chromosome, is in fact well underway. Los Alamos is about 60 percent complete—has about 60 percent completed a map of a particular human chromosome—human chromosome 16. These maps are much like highway or interstate maps, and I think you have heard already about the utility of such maps to rapidly identify disease genes.

A third accomplishment in the last year has been our ability to detect single molecules. This has been part of our advanced sequencing technology, and to put it in perspective, the identification of a single molecule is roughly equivalent to detecting much, much

less than a thimbleful of molecules in an Olympic-size swimming pool. I mean, this is a real accomplishment, and we hope this will lead to the kinds of breakthroughs you heard early, that in five years we will have, in fact, orders of magnitude better technology to do the actual sequencing when it comes time to actually do that.

What I would like to end with is really reiterating the point which has been discussed earlier. You heard about efficiency. I hope I have shared with you my excitement that there is no question in my mind that these maps can be produced in the next five years, given adequate funding.

The main issue is that most of the important human diseases—cancer, heart disease, many forms of mental illness, even relative longevity, are not the result of a single gene. Most of the successes you have heard about, such as cystic fibrosis, fall in that category. Most of the things that will in fact impact all of us are multi-genic. They are the result of many genes, and with current technology, no matter how much money you pump into trying to find that gene, you will be unsuccessful.

There is only one way to do it, and that way is to get a complete map. Then we have a hope of at least identifying all of these genes that will lead not in this century but really in our lifetime to individualized diagnostics.

I mean, I think, to again use another example, every time I pick up a newspaper, whether or not ingesting massive amounts of cholesterol is going to lead to heart attack is currently under debate, and I think the problem is that we are all individuals. You can just look around the room. We all have different hair colors, et cetera, and I think our susceptibilities to many diseases will be a very individualized thing.

What I would like to see is that in five or ten years, for many of these traits one can literally walk into a doctor's office and get that kind of individualized attention, not just for cancer but for many of the things that really we are all going to be affected by.

So I just want to conclude with saying this project is doable. I think we have got demonstrated evidence that it is doable, at least in the first phases, and I have ended my formal statement and I will end it here, I cannot agree more wholeheartedly with the statement that Jim Watson made that it is essentially immoral not to do this project, and really not to do it as fast as we can do it.

Thank you.

[The prepared statement of Dr. Moyzis follows:]

Statement of Robert K. Moyzis

Director

Center for Human Genome Studies

Los Alamos National Laboratory

Los Alamos, New Mexico

before the

United States Senate

Committee on Energy and Natural Resources

Subcommittee on Energy Research and Development

11 July 1990

Mr. Chairman and Members of the Subcommittee:

It is a pleasure to talk to you today about what is, I feel, one of the most exciting and challenging frontiers in the history of science, the Human Genome Project. This project, which will unravel the complete genetic information present in each one of our cells, will have unprecedented impact on our country and the world. The revolutionary understanding we will gain through this project will have profound effects on the quality of both medicine and our technological competitiveness, not in a century, but in our lifetime. It is the only, and I repeat only, way we will understand the genetic components of complex human disorders, ranging from heart disease, cancer and schizophrenia to the health effects of energy related technology. I hope to share with you today my enthusiasm for the Human Genome Project. In its short history at Los Alamos, this project has already produced exciting, novel and technologically useful results. The goals of this project are attainable, given adequate funding support. While discussing these successes, I will briefly address some of the recent criticisms targeted at the Human Genome Project.

History

The Human Genome Project at Los Alamos was initiated with modest funding in September 1987, when then DOE Secretary Herrington designated Los Alamos a Genome Center. This was a natural outgrowth of our previous work in experimental and computational biology. In addition, DOE possesses demonstrated competence in managing large multidisciplinary projects involving biological, biophysical, computational and engineering sciences, organized in the National Laboratory System. Examples include: 1) the National Laboratory Gene Library Project, in which laser-activated flow cytometric techniques, pioneered at Los Alamos, are used to identify and

sort individual human chromosomes for the construction of recombinant DNA libraries; and 2) GenBank, the national repository for DNA sequence data, and the National Research Resource for AIDS Sequences, pioneered by theoretical and computational scientists at Los Alamos. Today I will briefly discuss three major accomplishments of the Human Genome initiative at Los Alamos:

- The identification and cloning of the human telomere
- The mapping of over 60% of a single human chromosome
- The identification of single molecules by flow cytometry.

Background

Human DNA consists of 3 billion units of information. This information is present as strings of molecules called nucleotides, represented by the symbols G(Guanine), C(Cytosine), T(Thymine) and A(Adenine). The nucleotides of one strand of DNA are precisely paired through complementary hydrogen bonds with nucleotides on the other strand, so that A always pairs with T and G with C. This results in the well-known double helical structure for DNA proposed by James Watson and Francis Crick in 1953. The four nucleotides form the alphabet of the genetic code. The letters make up "words" (e.g., GGAATCAT) along each side of the DNA helix in "sentences" thousands of nucleotides long. These "sentences" are the genes, and the organizational information necessary to regulate them.

The genes are packaged into 24 distinct chromosomes. Each parent transfers one of 22 chromosomes called autosomes plus an X or Y chromosome to their children. Mutation or inappropriate distribution of genes within chromosomes results in genetic diseases, including susceptibility to many common disorders, of which cancer is an example. Techniques were developed in the early 1970s to isolate or "clone" small regions of human DNA in bacterial hosts. Biochemical and enzymatic techniques to

rapidly determine the sequence of nucleotides in these short regions of DNA were developed in the late 1970s. These breakthroughs in recombinant DNA and sequencing methods resulted in the explosion of biomedical and biotechnology insights currently in progress.

The Human Telomere

It has been one hundred years since the name chromosome was applied to the small worm-like cellular organelles containing the genetic information necessary to construct a human being. Fifty years ago, Nobel Laureate Herman J. Muller coined the term telomere to describe the ends of chromosomes, structures thought to be involved in the replication and stability of linear DNA molecules. The first major accomplishment of the Los Alamos Human Genome Project, within the first year of our program, was the identification and cloning of the elusive DNA sequences that tag the human telomere[1,2].

This discovery grew out of our interest in understanding the functional organization of human DNA. Mapping of human genes began early in the twentieth century, and has been pursued intensively during the last two decades. While the information to produce RNA and proteins is likely encoded in less than half of our genome, there is growing evidence that the remaining DNA is not all "junk". Rather, much of the remaining DNA is likely to function as the code for organizing, replicating, and controlling the readout of the information present in the protein coding regions. Identifying these regulatory and structural DNA sequences, and understanding the mechanisms by which they accomplish these functions, is, in fact, one of a number of long-range goals catalyzing the recent excitement in mapping and sequencing the entire human genome. To state that only the protein coding regions are important in DNA, as some critics have done, is analogous to the minority of 16th century biologists who thought the

human brain was "junk", merely because they could not think of a function for this remarkable organ! The human body is an amazing machine, with redundancy, yet little inefficiency, present in most of its design. The only human organ that is considered "junk" is your appendix, the remnants of a once useful component. It represents less than one thousandth of your weight. Yet if any of you have had an appendicitis attack, I'm sure you are delighted that physicians have not ignored detailed knowledge of this "junk" organ. It is naive, at best, to state that the bodies "blueprint", encoded in its DNA, is largely meaningless. Life, upon analysis, is more amazing and beautiful than any of us imagines.

Our discovery of the human telomere is a concrete example of this point. It is not a protein coding region. Its information content appears, at first inspection, to be minimal and redundant, consisting of repeating units of the sequence (TTAGGG). It would be dismissed as "junk" by the critics. Yet this sequence, the ends of the linear DNA in each of your chromosomes, confers at least two vital functions. First, prior to cell division, the two strands of the DNA double helix unwind and new complementary strands are synthesized, resulting in the exact duplication of the genetic information. If this process is defective, cells die or become abnormal, resulting in human diseases such as cancer. The telomeres are essential for completing this replication process. Second, it has been known since pioneering work in the 1930s that many environmental agents, from chemicals to radiation, can induce breaks in DNA. These induced "ends" or breaks in chromosomal DNA are highly unstable. They quickly recombine with other DNA molecules, producing mutations and human pathologies. Yet natural DNA ends are quite stable. These ends, or telomeres, "tag" a piece of DNA, sending a signal to the cell to keep it as a separate entity. This "junk" DNA, then, is essential to your survival. You would not exist without these sequences. It is vital we understand how they work.

An immediate practical application of this discovery to the Human Genome Project is our ability to define the end points of the human genetic and physical maps[3]. Current maps are similar to 16th century maps of the world, where some regions contain great detail, while others (The New World, for example) contain only hypothetical descriptions of the "ends" of entire continents. Until now, investigators have been blindly crawling along these genetic and chromosome maps, identifying DNA markers useful for the analysis of disease genes. Often, when a marker was thought to define the end of a particular chromosome, a new one was isolated that pushed the boundary millions of nucleotides farther away. The real boundary finally has been achieved. We now know nucleotide number 1 (the beginning) and number 3 billion (the end) of the human DNA sequence. Much like identifying all the end pieces of a jigsaw puzzle allows one to much more rapidly finish the puzzle, identification of the ends of the human "jigsaw puzzle" will greatly accelerate the completion of the human genome map.

Mapping a Single Human Chromosome

A second major accomplishment of the Los Alamos Human Genome Project in the last year has been the development of techniques to rapidly produce physical maps of human chromosomes[4,5]. Such maps, analogous to a detailed interstate highway map of the United States, will allow researchers to rapidly identify each of the 100,000 genes encoded in your DNA. The developments at Los Alamos included the coordination of novel biological, biophysical, computational and robotic techniques in a focused effort. This is a major strength of the DOE and Los Alamos efforts. This allowed us to "fingerprint" DNA clones, and assemble them into contiguous long (>100,000 bases) regions representing 60% of a single human chromosome (number 16). These DNA clones are pieces of human DNA inserted into either bacteria or yeast, where

they can be "photocopied" cheaply and in almost infinite quantities. Chromosome 16 encodes a number of important genes, including one whose mutation is responsible for adult polycistic kidney disease (over 200,000 potential cases in the USA). Our rapid production of these maps elicits enthusiasm that the 5-year physical mapping goal of the Human Genome Project, recently presented to Congress[6] is an achievable goal, given adequate funding.

This early practical success in physical mapping at Los Alamos allows me to comment on another criticism of the Human Genome initiative. It is claimed that this project is routine, boring work, and that it is "big science" taking money from "little science". The Human Genome Project is not "big science" when compared to other projects given that designation, especially in the physical sciences. Of course, certain aspects of this project are "big science", as defined by the biology community. That is as it should be. The only way to complete a physical map of the entire human genome is to have a focused multidisciplinary effort where many individuals participate. This is clearly the most efficient, cost-effective way to accomplish the stated goal. I have participated in both the cloning of individual genes and the initiation of mapping of entire chromosomes. I am convinced that a focused global mapping effort will be at least 100-fold more efficient than single investigators continuing to isolate disease genes independently. This is a natural and productive outcome of scientific progress. To use an analogy, while some may be saddened by their skills as a hunter being undervalued by modern food industry, few of us wish to spend all of our time hunting just to survive. Technology and specialization by a few, in this instance, has benefited all of society. I see no reason that biology and medicine will not benefit from the same focused approach, where it is appropriate.

An amazing thing is happening because of the "big science" Human Genome Project. Because of its complexity and scale, biologists at Los Alamos have found

great advantage in working side-by-side with their colleagues in the physical, engineering, and computational sciences. This interaction has produced novel solutions to the problems of complexity and scale, including robotics, automation, and computational algorithms that have freed humans from the "routine, boring" tasks the critics oppose. While it may be difficult to give up a hard-earned skill to a machine, the incredible increase in productivity, in fact, liberates one to pursue other innovative endeavors. Indeed, I have never seen morale so high as among those working on this project, where one can produce tangible, important results in a greatly reduced time. Further, the technology and data produced by this project will have immediate applications in "small science" as well as the biotechnology industry. The "spin-offs" are real. A number of patents have been awarded or applied for based on Los Alamos Human Genome work. Some of these innovations are already moving into the commercial sector. As an example, the image processing capabilities developed by Los Alamos computational scientists to help construct our "interstate" map of human chromosomes, have immediate applications in many areas, ranging from clinical diagnostics to criminal forensics.

The Identification of Single Molecules

A third area of excitement among Los Alamos scientists is our ability, in the last year, to detect the presence of a single molecule, using advanced laser and computational techniques. This project, part of our Human Genome technology development for rapid DNA sequencing, has progressed to the point where individual fluorescent molecules can be accurately identified. This is equivalent to detecting the presence of much less than a thimble full of molecules in an olympic-sized swimming pool. This technology will be applied to the rapid, inexpensive sequencing of large regions of human DNA, sequencing 40,000 bases or larger fragments at a rate of 100 to 1000

bases per second. The approach relies on fluorescent labeling of the bases in a single fragment of DNA, attachment of this labeled DNA fragment to a support, movement of the supported DNA into a flowing sample stream, and detection of individual fluorescently labeled bases as they are cleaved from the DNA fragment by an enzyme. The projected sequencing rate is based upon our experience with single molecule detection and known enzymatic cleavage rates. Just as important as the high sequencing rate is the ability to sequence large fragments of DNA. This will significantly reduce the amount of subcloning and the number of overlapping sequences required to assemble megabase segments of sequence information. An additional advantage of our approach is the elimination of problems associated with the disposal of radioactive materials and other hazardous wastes, such as acrylamide, which plague current sequencing efforts.

Why Pursue this Project?

All of these recent Los Alamos accomplishments are the result of initial funding for the Human Genome Project. My colleagues have addressed many of the important reasons for pursuing this project. I will conclude by addressing what I believe is one of the most important arguments for pursuing this project. Mapping the entire genome is the only way to obtain the most valuable information about our genetic individuality and susceptibilities. While some human diseases are the result of a defect in a single gene (the recent identification of the cystic fibrosis gene, for example), most of the economically important and devastating illnesses all of us will have first-hand experience with, are not. They are multigenic. They are the result of many genes. Heart disease, cancer, some forms of mental illness, and even relative longevity are just a few of these multigenic traits. When critics argue that they have no objection to funding research on individual genes, but oppose the Human Genome Project, they show a

complete misunderstanding of human genetics. There is no way to identify and isolate these important genes, except by producing a complete map. We cannot identify anything other than single gene defects (which are rare) with current genetic methods. With a complete map, however, with tightly linked genetic and physical markers, even multiple genes affecting a given disease (such as heart disease) can be identified. This will lead to individualized diagnostics. For example, simple genetic analysis might determine, for you, as an individual, whether reducing cholesterol intake will really have any significant impact on the likelihood of a heart attack. The technology and databases generated by this project will make such information available in this generation.

Another analogy may help clarify the problem. Current approaches to understanding human disease susceptibilities would be equivalent to Congress trying to decide the best course of action to reduce crime (or unemployment, hunger, etc.) in America by statistics obtained from one town in the Midwest with a population of 10,000. Even worse, imagine we have no knowledge that the remaining towns and cities even existed! Not only would we make inappropriate decisions with such extremely limited information, but any decision made would, in my opinion, have a chance of making things worse rather than better. This is the current limitation of human genetic analysis. Imagine allocating our entire available resources to this one small town, while the vast majority of the people we are responsible for receive no help at all!

There is a clear solution. You get information about all the people you represent. Only then can you identify the complex interactions and issues between various communities and groups. Likewise, the vast majority of human disease genes will not be identified, without first obtaining a complete map. Their isolation is the vital first step to a cure. I am confident, based on our early progress, that such a goal is obtainable.

Conclusion

As scientists, we are responsible to society to be "productively creative". Creative scientific ideas, produced with public funding, should eventually lead to benefits for mankind. No project in my lifetime will have as tangible an impact on medicine, biotechnology, and ultimately our society as the Human Genome Project. I am honored and feel privileged to be part of this endeavor, and thank you for your support. Given the enormous, straightforward potential of this project, I do not want to tell a single human being, afflicted with an incurable illness, that America did not obtain the knowledge that could have cured him or her, because we lacked the will to pursue this project. I agree wholeheartedly with Dr. James D. Watson, Nobel Laureate and head of the National Center for Human Genome Research at the National Institutes of Health, "It's essentially immoral not to get it done, and get it done as fast as possible".

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Senator FORD. Dr. Carrano.

STATEMENT OF DR. ANTHONY V. CARRANO, DIRECTOR, HUMAN GENOME CENTER, BIOMEDICAL SCIENCES DIVISION, LAWRENCE LIVERMORE NATIONAL LABORATORY

Dr. CARRANO. Thank you, Mr. Chairman, Senator Domenici. It is both an honor and a pleasure to provide my views regarding the human genome project, and specifically the effort at Lawrence Livermore National Laboratory.

As the other speakers have done, I am going to truncate my statement from the written testimony in the interests of time.

Senator FORD. Your total statement will be included in the record.

Dr. CARRANO. As Director of the Human Genome Center at Livermore I have been involved in the Department of Energy initiative from the earliest days in 1986 to the present. I have watched with fascination as my own research team assembled amidst the uncertainties. I now look back upon these earlier days with some amusement, and actually quite a bit of satisfaction. The uncertainties have been resolved in a positive sense, and previous critics have become some of our strongest advocates.

In addition, research progress has exceeded our expectations. The human genome program at Lawrence Livermore National Laboratory initially embarked on a modest effort to establish a physical map of human chromosome 19, which represents about 2 percent of the human genome. I am happy to report today that we have now assembled almost 60 percent of this chromosome as a set of overlapping DNA clones. A project that was once considered by our critics to be a mundane, repetitive effort, or even described as a punishment for scientists, has in fact been a delight, attracting some of the best minds in science.

Enthusiasm at Livermore has not waned. In fact, just the opposite. The pace and excitement is growing as we are increasingly able to localize genes on our map. For example, we have already identified and isolated genes involved in the repair of DNA damage. These genes recognize damaged DNA resulting from exposure to chemicals and ionizing radiation. They excise the damage and restore the original DNA sequence. Along with a number of collaborators, we are very close to identifying the gene on chromosome 19 responsible for a disease called myotonic dystrophy, a neuromuscular disorder which affects about one in 5,000 individuals. Identification of this gene should result in a set of biologics useful in early diagnosis and possibly in therapy.

I would like, now, to turn to two other subjects, namely the role of the national laboratory in the genome project and technology transfer. National laboratories, universities and industry each have unique advantages, and all have a role to play in this project. The national laboratories capture the intellectual freedom and diversity of talent that exist at a university. The research at these laboratories varies from specific, product-oriented, short-term applications to high-risk, innovative technology development, but all research falls within a defined, programmatic mission. In one sense, the na-

tional laboratories are a hybrid, capturing the intellectual richness of a university and the focus of industry.

A major asset, in my opinion, is that the national laboratories are multi-disciplinary and cross-fertilizing. For example, the genome project at Livermore draws upon biologists, chemists, physicists, mathematicians, computer scientists and engineers to fulfill its mission. All these disciplines flourish in our work-force, and the involved scientists are only steps away.

It is because of this diversity of talent, particularly in the physical and engineering sciences, that our technology transfer effort has been extremely active. In the last two years, we have established a substantive working relationship with at least six major U.S. companies including AMOCO, Applied Biosystems, Beck & Dickinson, Beckman Instruments, Life Technologies, and a start-up company called Autogen.

More specifically, we have transferred and/or licensed a variety of materials and technologies to include recombinant DNA materials and methods, innovative techniques in chemistry, computer programs for DNA analysis and storage, and instrumentation designs.

In addition to industry, the Livermore human genome program has established over 50 very active collaborations with scientists throughout the world. Foremost among these are our collaborations with the genome efforts at both Los Alamos and Berkeley.

Well then, what is needed to ensure the continued success of the human genome project and the maintenance of a national laboratory presence? First, I believe we must educate the public, Government officials and our scientific colleagues. We must help them to understand basic human genetics, the need for research in this area, the need for a focused human genome project and the benefits that will accrue. While this is everyone's responsibility, it is well suited for some of the educational programs being espoused by Secretary Watkins and the Department of Energy.

Second, at the laboratory level my most serious problems have to do with stability of funding and working space. I personally would like to see funding for this effort provided on a multi-year basis—for example, three to five years—with appropriate progress reviews built in. Space is also a major issue. We have consistently failed to achieve approval for a new building to accommodate the current level of about 25 staff on our project and the desired growth to about twice this number. We are now to the point where problems caused by overcrowding may indeed override our ability to progress satisfactorily.

Finally, there is a most important role for Congress. The human genome project can be done and will be done. Congress, via the budgetary process, will decide whether it will be done in 15 years or 50 years. I would hope that you choose the shorter time span, and provide the funding levels requested in the joint five-year plan. I truly believe that this is the most cost-effective approach to study the human genome.

That concludes my statement. Thank you for your attention.

[The prepared statement of Dr. Carrano follows:]

Statement of Anthony V. Carrano

Director
Human Genome Project
Biomedical Sciences Division
Lawrence Livermore National Laboratory
Livermore, California

before the

United States Senate
Committee on Energy and Natural Resources
Subcommittee on Energy Research and Development

11 July 1990

Mr. Chairman and Members of the Subcommittee:

It is both an honor and pleasure to provide my views regarding the human genome project and, specifically the effort at Lawrence Livermore National Laboratory. As Director of the Human Genome Project at Livermore, I have been involved in the Department of Energy effort from the earliest days in 1986 to present. I have watched with fascination as my own research team assembled amidst the uncertainties, including my own, of whether a project could be scaled to study the entire human genome, whether it could be coordinated at the national and international level, whether stable funding would be provided, and whether a team of scientists could be captivated with what was perceived by some to be a boring task. I now look back on these earlier days with some amusement and satisfaction. The uncertainties have been resolved in a positive sense and previous critics have become some of our strongest advocates. In addition, research progress has exceeded our initial expectations.

Before I discuss the specifics, let me state my general conclusions. There are three.

1. The human genome project has found its place in biomedical, health, and environmental research and has a stature which rivals and also complements some of our greatest national endeavors in the physical and engineering sciences.
2. The human genome project is cost effective and should be supported on a multi–year basis according to the recommendations proposed in the joint NIH/DOE five year plan. The support should be interdisciplinary encompassing mapping, sequencing, instrumentation, computations, and socio–legal studies. National laboratories, universities, and industry all have a role to play.
3. Scientists must properly educate the public, our government officials, and our colleagues on the scope and goals of the human genome effort with a view to heightening awareness and gaining acceptance of this national commitment.

Had I been asked to present testimony on behalf of this project two years ago, it would have reflected the uncertainties prevailing at the time. In the interim, however, technology, ideas, organization, and research have advanced so rapidly that substantial progress has indeed been made. At Livermore, for example, we have assembled a unique multidisciplinary team which is attacking this project with vigor. The investment is already paying handsome dividends.

The human genome program at Lawrence Livermore National Laboratory initially embarked on a modest effort to establish a physical map of human chromosome 19 which represents about 2% of the human genome. The goal we established was to construct a set of overlapping recombinant DNA clones for as much of this chromosome as possible. We were limited to an educated guess as to the speed, the accuracy, and the completeness with which this could be achieved because the only models which existed at the time were a bacterium, a yeast, and a worm. No one had attempted to assemble a human map over the scale the genome project required and there was much uncertainty about the comparative complexity of human DNA. Eighteen months hence we have shown that prudent application of then existing technologies and integration of emerging technologies has resulted in a better understanding of the human genome and allowed us largely to overcome or circumvent the potential barriers. I am happy to report that we have assembled almost 60% of chromosome

19 as overlapping clones. Barring the unforeseen, we hope to complete the chromosome 19 map, a much more difficult task, within the next couple of years. As we near our mapping goal for chromosome 19 and begin sequencing, we are willing to initiate work on another chromosome

A project that was once considered by our critics to be a mundane, repetitive effort or even described as a "punishment" for scientists has, in fact, been a delight, attracting some of the best minds in science. Enthusiasm at Livermore has not waned. Just the opposite. The pace and excitement is growing as we are increasingly able to localize genes on our clone map. There is no problem in motivating my staff to keep working. The difficulty, if any, is keeping ourselves focussed in the face of so much enthusiasm and research opportunity.

For example, we have already identified and isolated genes involved in the repair of DNA damage. These genes contribute to a multi–protein complex that recognizes damaged DNA resulting from exposure to chemicals or radiation. The repair complex excises the damage and restores the original DNA sequence. Our next step is to determine exactly how these genes function in the human and what consequences might ensue if the genes are defective.

Along with a number of collaborators, we are very close to identifying the gene on chromosome 19 responsible for a disease called myotonic dystrophy. Myotonic dystrophy is a neuromuscular disorder which affects about one in five thousand individuals. It is a dominant disorder, that is, it can be propagated to fifty percent of the children of affected parents. It appears late in life, generally after reproduction, and no diagnostic method currently exists to pre–identify those with the disease. Identification of this gene should result in a set of biologics useful in early diagnosis and possibly in therapy.

Finally, we are working to resolve a family of genes on chromosome 19. This family is now thought to contain at least thirty–five genes which are expressed during development of the embryo, are turned off during adult life, and re–expressed during the progression of certain tumors. This family of genes seems to be clustered in a small region of the chromosome. If we could decipher their underlying genomic DNA structure, we should gain insight into the mechanism by which these genes are regulated, that is, turned on and off. There appear to be other gene families existing on chromosome 19 and the almost daily addition of new clones, genes, or sequence information to uncharted regions of the chromosome provides both personal satisfaction and the stimulation to work harder.

I would like now to turn to two other subjects, namely, the role of a national laboratory in the genome project and technology transfer. I am frequently asked by colleagues, journalists, and lay people why a national laboratory is involved in this project. It is a good question. In my opinion, it reflects the fact that the public is inadequately informed regarding the role and capabilities of a national laboratory. I personally have worked in a university environment for over four years, have worked at three national laboratories over the past eighteen years, and during my career have worked very closely with industry. Each of these institutions has unique advantages and disadvantages and all have a role to play.

The national laboratories capture the intellectual freedom and diversity of talent that exist at a university. The research at these laboratories varies from very specific, product–ori-

ented, short–term applications to high–risk innovative technology development, but all research falls within a defined programmatic mission. In a sense, the national laboratories are a hybrid, capturing the intellectual richness of a university and the focus of industry. A major asset, in my opinion, is that the national laboratories are multidisciplinary and cross–fertilizing. The parts, or individual disciplines, act synergistically such that the whole is greater than the sum of the parts. While it is true that universities are also multidisciplinary, their organizational structure can be an impediment to highly interactive research.

The human genome project is and should be multidisciplinary. The program at Livermore draws upon biologists, chemists, physicists, mathematicians, computer scientists, and engineers to fulfill its mission. All these disciplines flourish in our workforce and involved scientists are only steps away. Biologists and chemists interact with the engineers and physicists to develop robots and image analysis instruments that minimize the workload or increase the sensitivity of a technique. Computer scientists learn biology so that they can properly provide the analytical tools that are needed to support the complex and voluminous data. In turn, our biologists have become computer literate because they are forced to use the computers to see the results of their work. We have only begun to exploit the mixed technologies that are necessary to capture a high resolution image of a DNA molecule by scanning tunneling microscopy.

Some would argue that this diversity is not necessary. To them I would respond that the diversity at Livermore has resulted in a very successful program and one that has been recognized and well received by our scientific peers. Moreover, it is because of this diversity of talent, particularly in the physical and engineering sciences, that our technology transfer effort has been extremely active.

In the last two years, our program at Livermore has established a substantive working relationship with at least six major U.S. companies. Several others are pending. More specifically, we have transferred and/or licensed a variety of materials and technologies. They include: recombinant DNA materials and methods that provide the researcher with state–of–the art tools for research in molecular biology, human chromosome–specific clones for use in the detection of chromosome damage or rearrangements, innovations in chemistry that allow the development and marketing of reagent kits for DNA analysis, computer programs for DNA analysis and graphical visualization of genome data, and electronic engineering designs that permit the fabrication of more efficient and sensitive instruments for biological research. These interactions with industry have been quite useful to our program and have progressed well. We will continue to pursue innovative ways of expanding them.

In addition to industry, the Livermore human genome program has established over fifty very active collaborations with scientists throughout the world. Foremost among these are our collaborations with the genome efforts at Los Alamos and Berkeley. For example, the National Laboratory Gene Library Project is a joint effort between Lawrence Livermore and Los Alamos National Laboratories. This project purifies individual chromosomes using a unique engineering technology developed at both laboratories. As a shared effort, recombinant DNA libraries for every one of the human chromosomes have been made and placed in a repository for distribution to qualified researchers. Thousands of copies of these libraries

have been distributed to scientists throughout the world. With Lawrence Berkeley and Los Alamos laboratories, we are exploring ways of constructing the next generation databases capable of handling the most complex data forms. In addition, we are working with them to exploit robotic technology for manipulating DNA.

What is needed to insure continued success of the human genome project and the maintenance of a national laboratory presence? Let me address this at four levels.

First, we must educate the public, government officials, and our scientific colleagues. We must help them to understand basic human genetics, the need for research in this area, the need for a focussed human genome project, and the benefits that will accrue. While this is everyone's responsibility it is well suited for some of the educational programs being espoused by Secretary Watkins and the Department of Energy.

Second, at the laboratory level, my most serious problems have to do not with scientific direction and progress but with stability of funding and working space. Lack of knowledge of the next fiscal year budget is a detriment to effective planning. I personally would like to see funding for this effort provided not on an annual but on a multi–year basis, for example, three to five years, with appropriate progress reviews built in. This is done in other research programs. Space is also a major issue. Construction funding to support biological research within the Department of Energy has been seriously lacking. We have consistently failed to achieve approval for a new building to accommodate the current level of about twenty five staff on our project and the desired growth to twice this number. We are now to the point where problems caused by overcrowding may override our ability to progress satisfactorily.

At the level of the Office of Health and Environmental Research, I see a critical manpower shortage. The reasons for this are complex and are common to many of our government agencies. The consequences, however, can impact negatively upon our local programs. Because the program staff in Washington cannot effectively recruit permanent high quality staff, it forces them to seek help either from the scientific staff at the laboratories who are then diverted from their primary research mission or from contracted groups who are less involved and often less motivated. The cost we pay is less attention to detail and overall degradation of quality.

Finally, there is a most important role for Congress. The human genome project can be done and will be done. Congress, via the budgetary process, will decide whether it will be done in fifteen or fifty years. I would hope that you choose the shorter time span and provide the funding levels requested in the joint five year plan. I truly believe that this is the most cost effective approach to study the human genome.

That concludes my statement. I thank you for your attention and this opportunity to speak.

Senator FORD. Thank you very much, Doctor. I have a couple of questions that I would like each of you to answer, and maybe it will not take too long. Let us suppose that one of the genome researchers at your laboratory makes an invention that he or she thinks a patent could be secured for that discovery. What happens? Who owns the patent? How does the technology transfer process work? Is our law governing the situation satisfactory, and could you explain that? Dr. Cantor, do you want to start?

Dr. CANTOR. Sure. First, I want to say that the type of example you are describing is happening all the time. We actually are working with no less than eight different companies on joint projects, and there will be inventions as part of those projects. The national laboratories are well set up to patent and protect inventions, and they own the patents and they license them to companies, and so this is really working very smoothly.

Senator FORD. So the law end of the situation you would say, as far as you are concerned, is adequate?

Dr. CANTOR. Yes.

Dr. MOYZIS. Likewise, there have already been two patents awarded and three in process just in the first few years of this project. It has been very easy, in fact. The laboratories, in general are I think very good at having a structure that encourages not only investigators to apply for patents, but getting those patents out to the commercial sector as rapidly as possible.

Senator FORD. Doctor.

Dr. CARRANO. Yes, I would concur with those previous statements. The patent system and the copyright system in fact does work. It requires a little pushing at time, but the mechanism is there to have it work and it does work.

Senator FORD. I have always heard we are very good at research and development and very poor at getting it into the marketplace. Once we do all the work and spend the money, somebody else has the ingenuity to move it into the marketplace.

Doctor.

Dr. MOYZIS. Having recently been at a university and having moved to a national lab system with all of our problems, I can unequivocally say it is probably a lot better where I am at right now. And that is a general problem, but I think the national labs in general do a much better job than most places.

Senator Domenici. Mr. Chairman, might I say in this area, I believe the statements, generally, that they have made are accurate. I think it is true, however, that we are doing better and there is room for improvement with reference to some of the relationships between the private sector and the national laboratories. But we are making headway and it is getting easier. And the collaboration and innovative ways of doing it are improving.

The last law that was passed cleared up a number of areas. I do believe that your question is most appropriate. And I must say there are still some areas, not necessarily in the areas they speak of, where this transfer of technology is somewhat difficult, but that is to be expected. It is a very complex situation of private versus public, academia versus the laboratories, but it is getting better.

Is that a fair statement?

Dr. MOYZIS. Yes, Senator.

Senator FORD. Let me then follow up a little bit on that one, Senator Domenici.

It is my understanding that you all can enter into agreements or consortia with private companies to do genome research cooperatively. How would the technology transfer process work for an invention made by a participant in a consortium with you?

Dr. CANTOR. Well, it is different in different cases, but I think what you do is you anticipate this before you set in motion such a consortium, and that you agree that the ownership is joint. So, in some of our collaborations with industry, if inventions are made and are patented, they will be jointly owned by the laboratory and the company. If you do not make these agreements in advance it can get very troublesome.

Dr. MOYZIS. Likewise, I think some of the ones that are being negotiated right now fall exactly into that category, and actually particular companies have a vested interest in being the first ones that develop a particular technology. And that is not an inappropriate way to do it.

You obviously want to try, however, to give everyone a fair shot at competing for the new technology that develops. And that is one of the things that we all deal with, of working effectively with, for example, a particular company to develop a particular idea, but giving everyone, really, a shot to have that opportunity.

Dr. CARRANO. I would concur. I think it is very important, as Dr. Cantor said, to define relationships right up front before any major interactions occur. And once that is defined, then the work proceeds very smoothly and ownership is proper.

Senator FORD. Let me ask you this now. Say we have a fantastic breakthrough, and so we have it patented. There is a joint ownership in that patent. There will be a royalty or whatever. Where does that money go that would come back for your half or your third or your 60 percent, whatever it might be? Where would that funding return to and how would it be deposited and used?

Dr. CANTOR. As far as I know, it would be returned to the laboratory and it would be used by the laboratory in any way the laboratory sees fit.

Senator FORD. Now that is not included in the budgetary process that we go through here. So if you have a patent that is bringing in money, that will be over and above what would be the budget from this body, is that correct?

Dr. CANTOR. Yes, that is correct.

Senator FORD. Is that the way you understand it?

Dr. MOYZIS. Yes. Presumably, it is my understanding also, that when negotiations are made, most patents are leased, for example, through at least the Los Alamos system, to a company, and there are mechanisms to try to get a certain portion of that money at least back to the original laboratory.

Dr. CARRANO. Senator, this is a very complex question that has a lot of complex answers to it. And it is one that is being actively discussed right now. The University of California has a patent royalty distribution policy in place which is being debated as being appropriate. As it stands at the present time, a portion of the royalties go to the University of California. The bulk of the royalties go

to, in our case, the national laboratories. And a small percentage of the royalties go to the individual investigator or investigators.

One of the issues is how much money do you want to give the original investigator. And you do not want to create scientists that are in the business of making money through royalties. You want them there because they want to do the science. And so the question of the distribution of royalties is an interesting one and one that needs to be debated and fixed in the near future.

Senator FORD. Do either one of you know approximately how much money comes back to the laboratory as a result of patents?

Dr. MOYZIS. There are other people in the audience from the lab who might be in a better position to answer that question.

Dr. CARRANO. I can speak to that for Livermore for the genome program.

Senator FORD. Well, what about other programs? We just started on the genome, we have not been after that but for three or four years, and you have not even gotten to the point where it may look good, but you are not feeling any green yet.

Dr. CARRANO. Yes, Senator, I think in the case of Livermore we are talking certainly less than $50,000 to $100,000 that is sitting in the fund right now for distribution as to the royalties, as to where they will be distributed. It is a very small amount of money.

Senator FORD. But there could be some big money in this particular program?

Dr. CARRANO. Yes, sir.

Senator FORD. Because when you grab the breakthrough and you start saving lives, and we do not have to worry about smoking cigarettes any more, well, you have got my money. [Laughter.]

The red flag just went up for me, Senator.

Senator DOMENICI. We will get the statute.

Senator FORD. Well, I wonder about how much is going there and how much is coming here, because taxpayers are funding a lot of what they are doing. And if there is a great deal more money, well, Dr. Watson could use a little more in some areas, and these gentlemen could use some more. But I personally want to be very careful that we do not get caught one of these days where you all are more commercial than you are taxpayers' researchers.

I am going to look into it a little bit deeper, so get ready.

Senator Domenici.

Senator DOMENICI [presiding]. Let me ask Dr. Cantor a question. We have recently spoken with Dr. Nancy Wexler, a prominent member of the research group on Huntington's Disease. And she states that after six years the gene for this terrible disease has still not been isolated. Could you please describe how technologies developed by the Human Genome Initiative will aid in finding this deficiency?

Dr. CANTOR. When the search for the Huntington's Disease gene was first started, we had only one piece of DNA in an enormous region. There was no map of the region. And much of the effort of the past six years was devoted simply to making a map of that region. One of the things which was particularly difficult is that there were no markers for chromosome ends. That is actually why we got interested in chromosome ends, and I think one of the reasons why Moyzis also got interested in chromosome ends.

Once ends of chromosomes were identified, one could then define the landscape in which the gene resides. And that is helping tremendously.

Another thing which is making that case particularly difficult is that the disease is actually quite rare. And so the number of different populations of affected individuals who have it is sparse. So the need for a good genetic map is particularly pressing for Huntington's.

Senator DOMENICI. Thank you very much.

Dr. Watson described the mapping with a degree of certainty that was refreshing for me. This question is for all of you. He then discussed sequencing, and he talked about the fact that there is a technology push occurring that he feels confident will dramatically change the development of the sequencing and substantially reduce its cost.

Now I cannot expect you all to speculate on cost, perhaps. But do you have any thing you could state for the record that would point in the direction that technology is indeed moving ahead with reference to sequencing, such that we may be able to do it much differently, and perhaps at much less the cost than is currently estimated? Do any of you know enough about that to talk to it?

Dr. CANTOR. I can start, because I recently did an exercise in calculating how much of an advance in sequencing we would likely get from five different developments which are currently underway throughout the world. So the worse case analysis, if these developments each sort of barely come to fruition, would give us something like a factor of two-to-five improvement in sequencing costs. And the best case analysis, if all of them work up to expectations, it would give us a factor of 40 decrease in sequencing cost.

Now I am not talking about blue sky developments. I am talking about very concrete optimization of existing methodology. For instance, there is a technique called capillary electrophoresis, which may enable you to read four or five times as much sequence in a single experiment. That is a factor of almost four or five in cost right there if that technology pans out, which is very likely.

Today's technology improved, which I think will almost certainly give us a factor of 10.

Senator DOMENICI. Doctor.

Dr. MOYZIS. Again, the three of us, as Dr. Watson mentioned, helped participate in the DOE–NIH five-year plan that Congress recently received. And I think what Charles has just said is reflected in that estimate that says a realistic five-year goal is to get the cost down approximately tenfold.

What I am encouraged by, though, is that especially the DOE has seen fit to try to accelerate even more novel approaches that will hopefully be the breakthrough ten years from now, where we can get the cost down thousands of fold. That is when sequencing will really move into the regime of a very routine medical procedure perhaps. And all three of the labs, again, have projects, one of which I alluded to in my discussion at Los Alamos, to do exactly that.

Senator DOMENICI. Doctor.

Dr. CARRANO. I think with the current commercially available systems in automated DNA sequencing, and the addition of robot-

ics that are just coming out to be able to handle the preparatory work, we are, by my calculations, at least within a factor of two of the target that was set in the five-year plan, which is 50 cents a base sequenced. And I think we are very close to that number at the present time.

There are new technologies, as Dr. Moyzis indicated, that have the potential, and they are being done at Los Alamos, and they are being done at Livermore and at Berkeley, as well, that have the potential of decreasing that cost a factor of 10 to 100. And so we might have some answers in the next four to five years as to the feasibility of these approaches.

Dr. CANTOR. Let me overscore one thing that the two others just said; the real goal here is not just to get one human sequence. That is a beginning and not an end. Because if you then want to study systematically human disease, you have to compare people.

So you need a very large ability, an ability to do very large scale comparative sequencing. And if we can reduce the cost of sequencing by a factor of 100 instead of by a factor of 10, then that brings into range a much more effective overall program.

Senator DOMENICI. Dr. Moyzis indicated in his own words the excitement that he feels about this project. Could either of you in your own ways, being experienced in various projects and programs, could you describe for the Committee, Dr. Cantor, why should we proceed with this program?

Dr. CANTOR. I think, in the long run, it is probably the most important piece of biology, as a nation, that we can do right now. Its impact will be so massive on medicine and biological science that it will truly be a landmark.

Senator DOMENICI. Dr. Carrano.

Dr. CARRANO. Well, I liken this project to the lottery. Why do people bet on the lottery? In a sense, the genome project creates a grab-bag of pieces of DNA. And we as scientists go in there and fish out the piece that has an important gene or gene of interest to us. That creates the excitement.

And there is a cost, economy factor, built in in doing that. Assembling that grab-bag, assembling those lottery tickets, basically, is the up front part; going in there and grabbing the pieces and the winning ticket is the excitement, and that is what keeps us going.

Senator DOMENICI. And you feel this program is going to dramatically accelerate the winning tickets over the piece meal approach now?

Dr. CARRANO. I believe the odds are infinitely better, Senator.

Senator DOMENICI. Is there anything we ought to be concerned about regarding the relationship between the NIH and the DOE, as you see it to this point? Is it satisfactory? Is there anything that concerns you? You have spoken to multiyear reliability.

Dr. CARRANO. Yes, I think that is one major difference between the two agencies with regard to this particular program. I think the relationship with NIH is going quite well. And I am quite pleased to see that. And the interactions with my colleagues that are funded totally by NIH have gone very well. And our advisory boards have gone extremely smoothly.

Senator DOMENICI. Senator Ford indicated at one point the concern that the United States makes the breakthroughs, other coun-

tries companies get the applications. It is obvious to me that one way we have got to minimize that is to make sure that projects of this type start with an interest, the laboratory interest, and a private sector interest, in some kind of mutual relationship of interest; and that will result in more opportunity for the final product to be used by a U.S. private sector entity under the rules of the game.

I do not know that you agree with that, but I have come to that conclusion. Assume that is the case: are private sector companies genuinely involved? And are they getting involved up front such that there is a chance that what results they would be—the result will interest them? And that it would be brought into the marketplace?

Dr. CANTOR. Well, companies are coming to me and saying, "what can we do together?" We want to work with you; we want to be involved. So I think the answer is emphatically yes.

Senator DOMENICI. And arrangements are being made within the context of the law?

Dr. CANTOR. Absolutely.

Dr. MOYZIS. Yes, I think that has been across the board, our situation, as the excitement grows on this project. I mean, not only the technology development ends and biotechnology companies, but as I think Charles mentioned earlier, the data bases and data that is going to be generated by this project are immense, and they need to be utilized by all of society. So many of the computing firms are incredibly interested in the impact of this project on the future of this country's medicine, for example.

Dr. CARRANO. I think there is no question that the companies have been coming forth. But I think the issue is they have been coming forth mainly in the areas of technology development, where they see a marketing scheme to be able to market a technology or an instrument. Where they have been more reticent, at least in the interactions we have had is in the usage of sequence information or clone materials. In a sense, are they really going to have a proprietary advantage in the use of sequence information? Are they going to be able to make something useful of it? And I think that is still an unresolved issue.

Senator DOMENICI. Would you not think that is rather natural that the former would be much more easily understood and the relationship much more easily created than the latter?

Dr. CARRANO. Very definitely, Senator. Yes, sir.

Senator DOMENICI. Well, we thank you very much, not only for your testimony, but for what you are doing. We appreciate it.

Dr. MOYZIS. Thank you for your support.

Senator DOMENICI. Next panel, we have Professor Davis from the Department of Microbiology, Harvard Medical School; we have a Professor Rechsteiner, Department of Biochemistry, University of Utah; G. Kirk Raab, President and CEO of Genentech and Dr. Lee Hood, Professor of Biology, California Institute of Technology, Pasadena.

Let me make this announcement. Dr. Rechsteiner from the University of Utah will submit his testimony, and we want to apologize to him. We rescheduled this hearing, in order to make sure we were able to do it, from this afternoon to this morning. And I

assume he was unable to make the connection, so we will make his testimony a part of the record.

[The prepared statement of Dr. Rechsteiner follows:]

Prepared Statement of Martin Rechsteiner

Mr. Chairman and members of the subcommittee, I thank you for this opportunity to present my views on the Human Genome Project. My name is Martin Rechsteiner, Professor and Co-chair of Biochemistry at the University of Utah. I am appearing before you principally because I believe the HGP represents an unfair and unwise allocation of precious research funds. These beliefs prompted me to start a letter-writing campaign against the HGP and to travel here today from Salt Lake City.

Five years ago I became Co-chair of Biochemistry at Utah. One aspect of my new position was to recruit young Assistant Professors and help them set up their research labs. This has proved both rewarding and frustrating. Rewarding in that we have attracted outstanding young scientists to the University. All have trained with members of the National Academy of Sciences at institutions including M.I.T., Stanford and UCSF. Our latest recruit is a student of Tom Cech, winner of the Nobel prize in chemistry. In short, Utah's new Assistant Professors are among the nation's best and brightest.

The recruiting process has also proved frustrating because I have witnessed the difficulties these talented young scientists have in obtaining funds for their research. I am sure you are well aware of the funding crisis at N.I.H. We have been experiencing the budget squeeze for several years now. While the annual 10-15% cuts were not pleasant, they were tolerable when we felt that we were all being treated equally. The HGP has changed these perceptions markedly. Now, in the worse funding year in decades, we see a proposal to disburse previously unheard of amounts of research funds to a handful of scientists. Who will receive the center grants? We don't know for certain, but it is clear they will know each other, for we are told in a recent Science article that finding reviewers for the centers will be difficult. According to Jane Peterson of N.I.H.'s National Center for Human Genome Research, "It would be easier if everyone wasn't interrelated" (1). Later she is quoted as saying "It is such a small community." There is even mention of having to send the applications abroad for review. Not surprisingly, the likely recipients of HGP funding are already established scientists. Their annual budgets are surely more than $1,000,000 whereas most of us are happy with $200,000 per year. It seems that a very small group of well-funded scientists will divide very large amounts of money.

How much new money is the HGP community likely to divide? Two hundred million per year? Proponents of the HGP emphasize how small a sum that is. Let me try to convince you how large it can appear. Two hundred million translates into more than 1,000 R01 grants from N.I.H.--or about seven grants for each major research university in the nation. When disbursed to the universities, those grants support a diverse collection of undergraduates, graduate students and post-doctoral fellows. Besides the actual scientific product from these grants, there is a tremendous educational benefit to the nation. By contrast,

diversion of the same funds to HGP centers will result in armies of technicians skilled only at obtaining DNA sequences and entering the results into computer data bases. At a time when a scientific career looks bleak enough, it makes no sense to compound the problem of recruiting scientists by restricting university grants. Because the future of U.S. biomedical research depends upon vigorous training programs, it is bad policy to fund cadres of technicians at the expense of university laboratories.

The proposed allocation of HGP funds is made even less palatable by the scientific justification for the project. According to Dr. Wyngaarden, the N.I.H. was spending $300,000,000 per year on mapping and sequencing disease-causing genes prior to the HGP (2). I support that effort and the relative allocation of N.I.H. resources that it entails. The HGP now proposes a 70% increase in budget for a crash program to sequence the entire genome. Many biologists believe that more than 95% of our DNA is junk, gibberish, nonsense. We believe it is there simply to properly space important stretches of DNAs that are the blueprints for the proteins that make up our bodies. We see no reason to sequence this spacer DNA--it is simply a waste of money.

Many of us also question the urgency surrounding the HGP. The genes for cystic fibrosis, muscular dystrophy, and numerous cancer-causing genes have already been located and sequenced. As yet, however, the sequences have not led to the development of effective therapies. We feel it is poor strategy to put so much money into obtaining more and more blueprints when we really need to discover how to build and repair the biological machinery. If every new sequence immediately saved lives, the urgency would be understandable. As it is, the sequences have not produced medical benefits. What we really need is funding in many areas to learn more about the workings of our bodies as a whole.

Thus far I have emphasized present resources and the necessity of making choices regarding their best expenditure. However, a most critical future resource is also threatened. That resource is our next generation of scientists. The Genome Project is in many ways an engineering project. The types of work that will be undertaken are developing faster DNA sequencing techniques, devising computer programs for storing and manipulating the data and turning the crank on sequence determination until all three billion base pairs have been identified and verified. This is basically repetitive, technical work that will not engage the imagination of our brightest prospective researchers. Some may be excited by the prospect of having the sequence available as a resource, but if training funds are eroded in the rush to determine the sequence, the scientists to use the information may not be around when the sequence is completed.

Finally, I would like to comment on the commercial benefits of the HGP. I am not a businessman--in fact, I have a knack for losing money. However, I cite Akio Morita, Chairman of Sony Corporation, who points out that information is not a product (3). I believe I know why. One has to steal Sonys one at a time. One has to steal DNA sequences just once. In fact, the sequences will presumably be readily available to foreign and domestic researchers. So what is the product? I suggest it is the Human Genome Project itself. Who is the prospective buyer? The U.S. Government. Who are the sellers? Proponents of the HGP. Will there be a lasting economic benefit to the nation? I seriously doubt it.

In closing, I again thank you for this opportunity. I regret that my message has been so negative. I am generally an upbeat person. Sometimes, however, one has to warn against those selling a bill of goods.

(1) Holden, C. (1990) NIH Left Peerless for Genome Centers. Science 247:1182.

(2) Anonymous (1988) Senate Committee Sees NIH/DOE Partnership in Genome Project. JAMA 259:15-16.

(3) Abelson P.H. (1990) America Bashing. Science 248:1173.

Senator DOMENICI. Let us proceed with the witnesses in the following manner: Dr. Hood, Dr. Raab and Dr. Davis. If you have prepared testimony, we have about a half-hour. You can either read it or excerpt it, but in all events we will make it part of the record at this point as if read.

Please proceed.

STATEMENT OF DR. LEROY E. HOOD, PROFESSOR OF BIOLOGY, CALIFORNIA INSTITUTE OF TECHNOLOGY

Dr. HOOD. It is a pleasure to be here and speak with you. I will abbreviate my testimony.

The human genome project, I believe, is catalytic both scientifically and economically, and it is a superb investment in the future. And what I would like to talk about are two striking benefits that argue compellingly for this investment in the future.

Number one, the human genome initiative is about developing new technologies. This is the first biological project that has as a major imperative developing new kinds of technologies. Molecular biology, although it is very sophisticated, has tasks that are routine and manual; and the genome project is now in the process of developing automated techniques for molecular biology, including those, as you have heard, for mapping and sequencing.

And perhaps equally important, the human genome initiative has brought to light critical new computational tools and approaches to fundamental problems in biology. Now the importance of this is, it is freeing up young investigators for creative and thoughtful analyses.

An extremely important point is that the imperatives of the human genome initiative are interdisciplinary; we have to bring together the technologies from applied math and applied physics, computer science, engineering, chemistry and biology. And, indeed, one of the major benefits of the human genome initiative will be to train a new generation of biologists that can handle these interdisciplinary techniques. And it is my belief that these people will be real leaders in biology in the 21st century.

As we all know, America is currently the world leader in biotechnology. This leadership is unequivocally being threatened by the Japanese. The human genome project, both through technology and the creation of a powerful infrastructure, is helping to insure this future world leadership. Let me make two points in this regard.

Number one, biotechnology offers America a real opportunity to redress our failure in industrial competitiveness and, accordingly, the negative trade balance. An example: in 1981, a small venture capital company called Applied Biosystems was initiated to actually commercialize several instruments for molecular biology that were developed in my laboratory. This company now employs 1,300 people. Today it is the world leader in molecular—instrumentation for molecular biology. Its profits last year were $180 million; 60 percent of these profits came from abroad; primarily from Japan and from Europe.

Hence, when we are technologically competitive, we can generate a positive trade balance. The human genome project to develop a

variety of new biological tools and technologies is going to spawn new industrial opportunities that will on the one hand create new industries and on the other hand will give the old industries new opportunities. And I would say that biocomputation will be one of the major industrial opportunities of the next 15 years.

Point number two is the biotechnology industry is not yet mature. It will not mature until the second or third decade of the next century. And what this means to me is, its potential is virtually unlimited, particularly if we keep in mind its applications to agriculture, to the environment, to animal health. And certainly it is an industry that is going to range far beyond the $100 billion range.

Hence, the human genome project will prime the American economic pump. It is a critical time to develop these new technologies. If we decline to do so, rest assured our competitors will fill the vacuum.

Point number two, and this is looking at what the genome can do for us in a slightly different way, is it is going to create a fantastic infrastructure for biology and medicine which will be centered on the map and the sequence of the human genome. As you have heard, the map is going to allow biologists and physicians to identify the genes that cause diseases very rapidly, and you have heard the example of cystic fibrosis. The estimate is today, it cost $150 million to identify and isolate that gene. With a map, we estimate it would cost $5 million to do it. That is a 30-fold saving. With the sequence, it will be considerably cheaper.

Hence, the real important point here is the genome initiative is going to let very small labs successfully compete with big labs in the mapping and identification of disease-causing genes.

Point number two about the infrastructure is the sequence is going to be the key to identifying our 100,000 or so genes. It is the key to identifying all of the proteins in the body. Once we have done this, we can begin to understand how complex systems, such as the immune system and even, in time, the nervous system function because we will have all the component parts. And as we do this, we will be able to develop molecular therapies that will use natural proteins as drugs to circumvent a variety of different diseases. And if we couple this with the DNA fingerprinting that will come from an identification of the genes, that will give us an unequivocal capacity to predict which of you are predisposed to particular diseases, if we put together the prognosis with the therapy, we will move America into a mode of preventive medicine.

My own area of research is autoimmune disease, and I am convinced in the next 15 years, we will be able to do DNA fingerprints on newborns and predict with unerring accuracy who is susceptible to arthritis, multiple sclerosis, or a variety of other diseases, such as diabetes.

More than that, we will be able to take these individuals, to appropriately manipulate the immune system, and to prevent them from ever getting the disease. To give you one specific example, rheumatoid arthritis costs American society $1 billion a year currently. Hence, the savings in this type of preventive medicine I think is going to be really striking. So, in closing, I would like to make the point that it is now the time for biology and the human

genome to grow together, to become mutually complimentary, and to lead biology and medicine into the 21st century, and I urge that you make this investment in American biology and medicine, and biotechnology, by approving the opportunities you have before us.

[The prepared statement of Dr. Hood follows:]

Statement of Leroy E. Hood

Bowles Professor of Biology and

Director, NSF Science and Technology Center

for Molecular Biotechnology

California Institute of Technology

before the

United States Senate

Committee on Energy and Natural Resources

Subcommittee on Energy Research and Development

July 11, 1990

I am here to strongly support the proposed budget increase for the Department of Energy in support of the Human Genome Initiative.

The Human Genome Initiative is a landmark scientific effort to map the human chromosomes, decipher their genetic instructions and develop the necessary tools and technologies to achieve these objectives.

Others have already told you about the extraordinary scientific promise of the Human Genome Initiative.

- It will allow us to find the genes involved in more than 3000 diseases, including Alzheimer's Disease, diabetes, autoimmune diseases and many nervous diseases.
- It will allow us to identify all the proteins in the human body and use many as natural drugs for therapies against cancer, infections and genetic diseases.
- It will help assure us of a world leadership in biotechnology.

In the federal budget, there are many competing proposals. However, I must stress that the Human Genome Initiative is catalytic, both scientifically and economically. The proposed Department of Energy genome budget increase from $26 million FY90 to $46 million FY91 is a compelling priority that must be funded, even at the expense of other alternatives, because it makes a superb investment for the future.

The Human Genome Initiative provides two striking benefits that argue compellingly for this investment in the future.

1. Technology

The Human Genome Initiative is about developing new technologies.

The Human Genome Initiative is the first major biological initiative that has had technology development as a major imperative.

Molecular biology is sophisticated conceptually, but the routine tasks are repetitive, manual labor. The Human Genome Initiative is developing many automated techniques for molecular biology, including those for mapping and sequencing. In addition, thanks to the Human Genome Initiative, critical new computational tools for biology are being invented and the most sophisticated approaches in modern computer science are being applied to biology.

The technology imperatives of the Human Genome Initiative require interdisciplinary efforts, bringing together the techniques of chemistry, computer science, engineering, applied math, physics and biology. The complex problems of modern biology demand these interdisciplinary collaborations and the Human Genome Initiative has been catalytic in this regard. Moreover, the Human Genome Initiative is training a new type of interdisciplinary biologist, who understands technology as well as biology. I believe these multidisciplinary biologists will be among the scientific leaders of the twenty-first century.

America currently is the world leader in biotechnology. This leadership is being threatened by the Japanese. The Human Genome Initiative, both through its technology and the creation of a powerful biological infrastructure, will help ensure this world leadership in the future. In this regard, let me make two points. (1) Biotechnology offers an opportunity to redress America's failure in industrial competitiveness and the negative trade balance. Let me give you an example. In 1981, a small, venture capital supported company, Applied Biosystems, Incorporated, was initiated to commercialize several instruments for molecular genetics that

our laboratory had or was developing. This company now employs 1300 people. Today it is the world leader in instrumentation for molecular biology. Its profits last year were $180 million. Sixty percent of these profits came from abroad, primarily from Japan and Europe. Hence, where we are technologically competitive, we can generate a positive trade balance. The Human Genome Initiative promises to develop a variety of new biotechnology tools and technologies that will in turn spawn new industrial opportunities, both as new companies and as new directions for established companies. Indeed, I would predict that biological computing will generate striking new industrial opportunities in the future. (2) The biotechnology industry will not mature until the second or third decade of the twenty-first century. Hence, the growth potential of the biotechnology industry, in my view, is virtually unlimited - particulary keeping in mind the potential for agriculture, animal medicine and the environment - certainly well above the $100 billion range.

The Human Genome Initiative will prime the American economic pump. It is a critical time to develop new biological technologies. If we decline to do so, rest assured that our competitors will fill the vacuum.

2. Infrastructure

The Human Genome Initiative is about building an infrastructure for biology and medicine - first, assembling an ordered array of DNA fragments across the human chromosome (called the map); second, deciphering the genetic messages of the chromosomes (called the sequence); and finally, developing the automated technologies and computational tools necessary to create the map and sequence.

The map will allow biologists and physicians to find the thousands of genes causing disease more rapidly and much less expensively. For example, it is estimated that it cost $150 million to

isolate the gene for cystic fibrosis. With a detailed map of the human genome, this cost could easily fall below $5 million - a thirty-fold savings. With the sequence, it would cost considerably less. The map also will allow small laboratories to compete with large labs in the mapping of human genes.

The sequence will allow the identification of the 100,000 or so human units of information (genes), and will allow the identification of specific genes that predispose us to cancer, autoimmune disease, heart disease and nervous diseases. Moreover, the identification of all the human proteins will give us the tools to understand how the immune system, cardiovascular and eventually the nervous system function. These understandings will lead to new therapeutic strategies, so that DNA fingerprinting, which will allow us to predict disease susceptibility, can be joined to therapeutic approaches to prevent the corresponding disease - thus ushering in an era of preventive medicine. Let me give you an example. Our investigations of human autoimmune disease lead us to suggest that in 15 years we will be able to predict from DNA fingerprints who will be susceptible to diabetes, rheumatoid arthritis or multiple sclerosis, and then we will be able to prevent, by manipulation of the immune system, the onset of these diseases. Since rheumatoid arthritis alone costs Americans approximately $1 billion per year, the savings of preventive medicine will be enormous.

The automated technologies and computational tools will free biologists and physicians for more creative activities. For example, automation allows a single biologist to sequence DNA approximately 1000 times faster today than just twelve years ago. Furthermore, the time spent on this laborious task is greatly decreased. Thus, young scientists can gain access to far more information and free up more time for creative thinking or interactions.

3. Inappropriate Concerns About the Human Genome Project

The naysayers to the Human Genome Initiative argue that it is bad science, big science, an inappropriate educational environment for young scientists, and that it competes with traditional biology for support.

- Bad science - The opponents misunderstand the goals of the Human Genome Initiative. The creation of powerful new automated technologies and computational tools, as well as the infrastructure provided by the map and sequence of the human genome, is good science. Most opponents argue that sequencing is expensive and hence it would be ridiculous to sequence the entire genome now. This is true. Realize that most of the human sequence analyses will be carried out only after we have sequencing tools 100-1000 times more rapid and about 100-fold less expensive than contemporary methods. Then sequencing the human genome will become an incredible biological bargain.
- Big science - The Human Genome Initiative primarily funds single investigator sponsored research. It is not big science. Rather, by making the human chromosomal map and sequence available to small laboratories, it allows them to compete with large laboratories. Hence, the Human Genome Initiative is the guarantor of small science. Equally important, it encourages a new type of biology that employs technologies from many other sciences. Rather than big science, it is interdisciplinary science.
- Poor training environment - The Human Genome Initiative offers exceptional training opportunities. It will free young scientists from the drudgery of molecular biology by automation and new computational tools. Young scientists will have access to enormously increased amounts of information; hence, they will

have more opportunity for thoughtful and integrative activities. Finally, the young interdisciplinary scientists will lead biology and medicine into the twenty-first century.

- Competition for funds - The naysayers view the Human Genome initiative as inappropriately competitive with conventional biology. This situation is similar to the view many biochemists had toward the emerging molecular biology in the late 1960s. The biochemists were by nature conservative and felt uncomfortable with the changes molecular biology represented. Moreover, they failed to understand the power of molecular biology and completely failed to envision the revolution in biology arising from molecular biology. In the end, molecular biology and biochemistry reinforced and enriched one another. Both are essential to contemporary biology. So the Human Genome initiative promises to enrich contemporary biology through revolutions in technology and the creation of a powerful biological infrastructure. It is time for biology and the Human Genome initiative to grow together and become mutually complementary, leading biology and medicine into the twenty-first century.

I urge that you make an investment in the future of American biology, medicine and biotechnology by approving the requested increase for DOE.

Senator DOMENICI. Thank you very much, doctor. I might just, as a matter of personal privilege, editorialize. It is indeed refreshing to hear a distinguished professor from a distinguished university speak as you just have, because I do not think we frequently enough hear from people like you about the application of research to America's economic future. In this case, it happens to have a magnificent duality, because on the one hand, you are quick to address the fact that it will mean much to America's economic future because we are the leaders in this field and we might stay there, and it is an enormous part of our economy. At the same time, you are addressing the issue of wellness, preventive medicine, and cures, and I compliment you for it.

As a matter of fact, I am of the opinion that more of America's academic leaders are going to have to begin to think this way, and speak this way, and I know many of them will think I have no justification to speak such and enter into their sacred field of academia, but I feel very comfortable saying it. We will not be able to afford the academic infrastructure of the past if we do not, and if it does not come from people like you who are cognizant of it, I do not know where it is going to come from. And so, I thank you for that.

Mr. Raab.

STATEMENT OF G. KIRK RAAB, CHIEF EXECUTIVE OFFICER AND PRESIDENT, GENENTECH, INC.

Mr. RAAB. I am not a doctor, I am a businessman and I think I am the one person speaking today who is not a scientist, is a businessman, and I feel very privileged to be with such a group of outstanding scientists, and Lee Hood, who I have known for many years, I think what I will have to say briefly to you compliments what he has just said.

I am President and Chief Executive Officer of Genentech, which is the largest and oldest biotechnology company, and we have discovered and developed four of the six biotechnology products that are on the market in the United States today. We have been able to do that because of the funding of the United States Government to the NIH and the great research and developments that have come out of that funding, and it is just the beginning and that is what we are talking about today, is just the beginning.

At Genentech, we are working on cancer, AIDS, infection, heart disease, arthritis, asthma, and cystic fibrosis, which has been addressed today. In fact, we have announced recently a product that will not cure, but certainly will alleviate many of the problems, we believe, in cystic fibrosis. We support 100 percent of this effort, and I briefly want to tell you why.

First, speed. The speed which this will give us to solve problems can be likened to what has happened with the computer sciences, and what we can do today, as compared to just five and 10 years ago, the speed of science is tremendous, and the ability to use technicians rather than scientists to make things happen.

Second is the breadth. I see this as a dictionary. I have learned several foreign languages, and I cannot imagine having studied both the spoken and written language without having a dictionary in hand, and that is, to a certain degree, what we are doing today,

and what the goal is for us to have a dictionary, so we can do this discovery and research so much better and faster.

Third is that it is ongoing. It is not like many of the other so-called big science projects, where the real significant benefits happen at the end when it is finished. From the beginning, including right now, we are reaping ongoing benefits from this program.

The dimension, it is immense. Private enterprise can do some, and we are doing some, but there is no way that we could do a project such as this. We need the United States Government to do it.

Next is advance, that we cannot do this alone, we must do this together as a cooperative effort, and I think the style of the program between the DOE and NIH is the right way to do it.

Health care progress—I do not think I have to comment on that. It has been well stated by scientists and physicians that you have had here before you today.

The final point I will make is American industry. This program will employ, will benefit industry through employment, significant employment. It is and will. It will benefit because of the scientists that come out of the program. Most of our top scientists were at the NIH before they went into academia or directly into Genentech, and this program will provide more and more scientists that can come into American industry, whatever their nationality, from the program and help us grow.

Third is the exports that Dr. Hood mentioned. The pharmaceutical industry has been a positive export, a balance of trade industry for many, many years, and this will enable us to be even a more positive contributor to our balance of trade.

And finally, profits. Because when we have profits, we pay taxes, and so I am not sure anybody can calculate whether the taxes that will be reaped from this program will eventually pay for it. I believe in time they will, and I think that is worth while.

I would like to close by saying that I think our government has a major opportunity to advance not just the length, but most importantly, the quality of American life in a very short period of time. Thank you.

[The prepared statement of Mr. Raad follows:]

TESTIMONY OF G. KIRK RAAB

CHIEF EXECUTIVE OFFICER
AND PRESIDENT

GENENTECH, INC.

ON BEHALF OF

THE INDUSTRIAL BIOTECHNOLOGY ASSOCIATION

Summary:

The Human Genome Project is worthy of Federal support. It will produce tangible social, economic and health benefits, including greater pace and efficiency of research into the treatment or cure of genetic and non-genetic diseases.

Introduction:

My name is Kirk Raab and I am the President and Chief Executive Officer of Genentech, Inc. I am testifying here today on behalf of both Genentech and the Industrial Biotechnology Association (IBA). The IBA is a trade association consisting of over 100 companies in the biotechnology field.

Genentech is the world's largest biotechnology company, specializing in the discovery, development and marketing of recombinantly-derived human pharmaceutical products. Four (4) of the first six (6) biotechnology derived products approved for marketing by the Food and Drug Administration were created by Genentech scientists.

I am here today to address a fundamental question. What role, if any, should the government play in mapping and sequencing the human genome?

My answer is straightforward. The Federal government should actively support the Human Genome Project. This project offers us a unique opportunity to expand our knowledge of human physiology. At the same time this initiative can, I believe, provide substantial benefits to the American biotechnology industry.

Background:

When Genentech was founded fourteen years ago by a young scientist and a younger venture capitalist, there was no biotechnology industry. In the past decade and a half the pace of change in the world of science has been dazzling. We have seen what -- according to the National Academy of Engineering -- is one of the greatest engineering accomplishments of the past 25 years: the discovery of drugs derived from human proteins. By the end of this century virtually every drug developed will, in some

manner, be touched by the tools of biotechnology.

This dramatic growth in biotechnology is a testament to the foresight of the Federal government. The Congress in its wisdom has consistently provided generous funding for basic research, especially in the health context through the National Institute of Health. The government has also assisted in the transfer of technology from the government to the private sector through a series of important legal changes, including reform of the government patent policy.

The current products of biotechnology already on the market include human insulin, the antiviral alpha interferon, a hepatitis B vaccine, the heart attack drug -- tissue plasminogen activator, human growth hormone, a drug that prevents kidney transplant rejection, and the anemia drug -- erythropoietin. These drugs have saved or improved the lives of hundreds of thousands of Americans as well as hundreds of thousands outside of the United States.

As a practical matter, it would not have been possible to develop these new biotechnology derived drugs without the assistance of government funding for basic science research. In many important ways the funding of the Human Genome Project is a continuation of this government commitment to basic research. We in the biotechnology industry fully expect many of the same concrete benefits of this project to have real world, commercial application.

We expect that the Genome Project will produce the following benefits:

* Knowledge of the human genomic map facilitates more rapid identification of genes involved in human genetic diseases. While more than 4,000 genetic diseases have been defined, very few of the genes have been identified.

* Mapping and sequencing the genome will enable scientists to better understand the genetic differences between individuals. Humans differ from one another by approximately 1/10 of one

percent of their nucleotides. These differences make virtually every human being (except for identical twins) distinct from one another. Genetic differences may have substantial medical implications if they are associated with the mechanisms that play important roles in protecting humans against disease. Genetic differences within this mechanism appear related with such auto-immune diseases as diabetes and multiple sclerosis.

* Mapping and sequencing the human genome may also help scientists better understand cancer cells. Cancer cells differ from normal cells in that they reproduce in an uncontrolled manner. One of the keys to understanding cancer is to determine the reasons for a cancer cell's uncontrolled growth. Studying the human genome may enable scientists to determine the role certain genes play in the development of cancer.

* The information obtained from these projects will accelerate the pace and efficiency of research, and as a result its application by the biotechnology industry will be enhanced.

To quote from the Office of Technology Assessment Report on the Genome Project:

> Advances in the development of human therapeutic products will be made more rapidly if research in the areas of protein engineering, the relationship of protein structure to function, ... [and] rational drug design ... parallels genome mapping efforts.

The creation of a sourcebook for biomedical science should also have some important benefits in other fields of science as well. As my colleagues on the panel know, the development of mapping and sequencing technology involves extensive interdisciplinary cooperation. One likely by-product of this process are improvements in computer science and software development. There are also, according to the Office of Technology Assessment, other benefits in the study of molecular evolution. If we ever hope to reconstruct the history of life on this planet, then the definition of gene families and the search for a universal ancestor all require an understanding of the

organization of genomes.

In light of this rosy scenario, why does this project remain controversial?

There appear to be at least five major areas of conflict. Let me briefly touch on each of these issues.

Ethics:

The Congress of the United States needs no reminders of the importance of ethical issues in the public policy debate. There are many important -- and profound -- ethical, legal and social questions posed by genome research. Many, if not most, of these questions predate any genome initiative at the Federal level. Nonetheless, with the antiseptic of public scrutiny that attaches to any new Federal program there is renewed interest in ethical issues.

Fortunately, Congress and the Administration have been sensitive to these concerns. The Office of Technology Assessment,

an arm of the Congress, has completed, or underway, numerous relevant studies. Congressional hearings have been held on many of the key issues, and more will occur as the science progresses. Most notably, as a part of the Human Genome Project, Dr. Watson has devoted at least 3% of the project budget to the study of ethical questions that arise out of this undertaking. This initiative should be applauded. For public support to be maintained for basic science, we must educate and involve the public in the debates about the future uses of biotechnology.

Organizational Structure:

As I understand it, there are some who remain concerned about the bureaucratic prerogatives of managerial control. When the IBA last submitted testimony on this subject, we urged the Congress to assure a prominent role for the National Institute of Health. In our view, the efforts of Jim Wyngaarden and Jim Watson have accomplished that goal.

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Big Science:

There has been an unfortunate tendency in the public press -- and among some elements of the scientific community -- to label the Genome project as BIG SCIENCE. These same individuals usually proceed to set up a three legged straw man consisting of the Human Genome Project, the superconductor/super collider, and the space station. Whatever the merits or demerits of the other two projects, the genome project is not big science. This is so for several important reasons. First, its budget is dwarfed by the other projects. For example, the Space Station project is projected to cost over $30 billion -- or approximately ten times the Genome budget. Second, it is likely that the largest genome center will employ between 30 and 50 employees -- hardly the scale of Apollo or the Manhattan project. Third, the success of the other two projects will only occur after total completion and operation of a physical structure; whereas the Human Genome Project is already producing tangible human health and economic benefits. Finally, and most importantly, even without a genome initiative some level of activity in this field would continue.

The only question is whether this diverse research field should be nurtured and coordinated to maximize societal benefits.

Money Drain:

Within the last few years, there has been a considerable amount of concern expressed about the relative level of funding for NIH projects. I believe that I speak for the entire biomedical establishment when I express agreement with this concern. In recent months, the IBA has taken steps to advocate increased funding for NIH. We, as a company, have raised this issue directly with the Vice President, and his Council on Competitiveness. I am hopeful that the Administration and the Congress will address the level of NIH funding.

I must hasten to add, however, that the mere existence of the genome initiative is not the cause of NIH's funding problems any more than is AIDS. It is unfortunate in the extreme that this time of fiscal restraint that advocates for basic scientific research are fighting over an ever diminishing piece of the fiscal pie. Rather, I would hope that we could make common cause

to present a unified front in support for adequate funds for basic biomedical research. This positive approach is the very tack that RESEARCH!AMERICA -- founded by your former colleague, Senator Weicker -- has taken.

International Competition/Cooperation:

The final area of conflict has been the appropriate role of foreign governments and scientists in the genome initiative. There is a degree of schizophrenia on this issue. On the one hand, we want to make sure that an effort that will ultimately benefit all mankind is funded by governments outside the United States. On the other hand, we want to avoid falling into the trap of presenting a foreign state with a competitive advantage because of their sometimes superior ability to commercialize the result of basic research.

In general, I believe that there are several principles that should be applied to assessing the question of international competition.

First, our relationships must be based on basic notions of reciprocity and national treatment. By that I mean that foreign governments must treat our nationals at least as well as they treat their own. This equal treatment must be measured in terms of actual results, not merely in terms of "legal" equality or vague commitments.

Second, our relationships with foreign governments should be premised on the linchpin of scientific inquiry that open networks of communication ultimately serve the public interest.

Finally, in allocating government resources we should pursue self interest "rightly understood". This means that great attention must be paid to facilitating the transfer of technology issues and the commercial spin-offs of this project.

Conclusion:

Thank you for providing us with the opportunity to testify here today on behalf of Genentech, Inc. and the Industrial Biotechnology Association. We look forward to working with the Committee in the months ahead in fashioning improvements in the Human Genome Project.

Senator DOMENICI. Thank you very much. Dr. Davis.

STATEMENT OF DR. BERNARD D. DAVIS DEPARTMENT OF MICROBIOLOGY AND MOLECULAR BIOLOGY, HARVARD MEDICAL SCHOOL

Dr. DAVIS. I am pleased to be here, and I want to note that my written statement has been endorsed by a large majority of the members of my department and also by the members of the Public Affairs Advisory Committee of the American Society of Biochemistry and Molecular Biology.

I am in the unenviable position of presenting a minority, critical view with respect to what has been presented here, and most of what has been presented to the world about this project. I therefore want to emphasize that I think it very much a majority view as far as the biomedical community is concerned, and so I hope I can take a few minutes to to give the reasoning behind this view.

The human genome project had an unusual origin. It was not something that had to come about because scientists recognized that we have reached a stage where we had to have it. It received its real push from an administrator in the Department of Energy who saw an opportunity for a large program that would be valuable, and that it was time, perhaps, for biology to enter the era of big science. However, biomedical scientists have been impressed by how much the astounding success of their field has depended upon individual investigator-initiated grants. They have not been very happy, I think, by and large, at the prospect of big science entering. Certainly the necessity for big science in biology is not the same as it is in physics, where you have to have enormous instruments that you simply cannot have without it.

Nevertheless, when the project proved politically invincible and the NIH joined it and became, logically, a major partner, there was very little grumbling from the biomedical community, although I suspect that there was a lot of feeling then that there were dangers in introducing big science into our field.

Since that time, several changes have occurred that have led to the growth of a serious concern, which is beginning to emerge in print. First, there has been a crisis in funding of new grants at the NIH, while this project, on the other hand, is rather insulated and growing rapidly. Secondly, there has been a radical change in the content of the program. And thirdly, despite this radical change, not all of which by any means needs centralized direction, the program has inherited the framework that would have been necessary for the first program. For clearly the original aim of sequencing from A to Z would have required a centralized program.

Now, I realize that the crisis in NIH research funding is not the primary concern of this Committee, and that the content of the program is a much more important thing to discuss. But I believe that the perception of competition between the human genome project and NIH research funding clearly adds a great deal to the intensity of current criticism of the project. More important, this perception has serious consequences for the future of science in this country, which I will come to in a moment.

What is the size of the crisis? I am aware of the fact that the total number of grants has gone down in part because grants have become longer. But there are a number of other factors, Dr. Watson mentioned the large number of exciting projects coming up. Another is that the average grant is more expensive. But the most important fact is that a decade ago some 40 percent of approved grants were being funded while, today in some study sections it is less than 15 percent: so whatever the rule of various factors, the underfunding is serious. This has created tremendous resentment and uneasiness in the scientific community.

The most important consequence, I believe, lies in the area of long-term implications for science and technology in this country, and therefore for our economic welfare. An atmosphere in which bright young science students see their respected professors extremely nervous about whether they can continue excellent research is not an atmosphere that will encourage the young people to seek scientific careers.

We read about prospective shortages of scientists in this country, and I do feel that we must consider the possible demoralizing effect of divisiveness in the scientific community over this issue as one that may have serious consequences for the advance of science.

Is there really competition between this project and the RO-1s? It is very difficult, or impossible, I would suspect, either to prove or disprove. It seems hard to doubt that in times of financial stringency, which has become much tighter today than when the project was first proposed, the bottom line must loom very large in your concerns over how much to spend on this and how much on that. It is therefore widely believed in the biomedical community that this project, which started as an extra, to some degree inevitably competes now with the extremely stringent funding in the NIH for new grants.

What is the scale of the project compared with the other grants? It is not negligible. The total untargeted NIH grants now add up to about $4 billion a year, and what is planned for the genome project, as we know, is about $200 million a year. That is equivalent to 5 percent of all biomedical research, which is quite substantial for a single, general program.

Even apart from the question of competition, the insulated and rapidly growing nature of this program creates, as I have said, resentment—not only in terms of fairness, but in terms of evaluating the return on the investment in the various areas being supported. The latter is what I would like to spend a couple of minutes on right now.

Tthe program, as you know, has changed very much from A to Z sequencing into a mixture of other activities. Mapping is the most important, but there is also research on sequencing methods, data processing, sequencing regions of interest, and including other organisms from bacteria to the mouse.

These are all excellent goals. But except for the mapping I would suggest that they are what we would be doing today if there were no human genome project. We would be doing all of these things through competing grants, though no doubt on a smaller scale. If this project were to be submitted today as something new, without the history of the original political appeal of the very definite goal

of something like putting a man on the Moon—getting that last human nucleotide—if it were to be proposed today as a new project, it seems doubtful that it would generate the same political appeal that the original one had.

Now, if we look at specific parts of the project, the mapping of signposts is certainly very valuable for the diagnosis of monogenic diseases. But on the whole these are very rare diseases, as you have heard. So however valuable it is, it is not self-evident to many people in the community that it is worth a very expensive crash program.

I understand Dr. Watson's enthusiasm for saying we must move ahead as fast as possible in order to get the answers quickly to problems like cancer. The question is whether this is going to be the most effective way to get at such problems as cancer.

The systematic sequencing has been postponed, to be reevaluated five years from now, and it may well be that by that time it will not seem important. For the most fruitful approach to understanding the genome is to link sequences to function. Now, identification so far has started mostly with studies of function. It is not hard to go from the known structure of a protein like hemoglobin to identifying its gene, and huge new areas of promise are benefiting from this approach. In developmental biology, there are tremendous breakthroughs in identifying genes that direct a part of an early embryo to become an arm or a leg. In neurobiology, we are beginning to identify key genes in neuro-function. In immunology, any number of specific factors are being discovered and each in turn is being traced to the corresponding gene.

The reverse approach is to discover a sequence and then try to find its function. I am not an expert in this area, but I gather it is generally agreed that it is much more difficult to take a sequence, even one that looks as though it is a sequence designed to make a protein, and then go from that information back to function. In addition, there is the major problem of all the so-called junk that is there. Undoubtedly, much of it is not really junk but has functions that we cannot yet identify, such as keeping the six feet of DNA in each of our cells from getting tangled in going through its paces.

This is a major challenge to biology which surely will have to be approached by studying sequence—but not necessarily 3 billion nucleotides of sequence, because that unknown function of the junk is going to be very much the same in every chromosome. It is going to be detailed study of a sample of that junk that will lead to the answer, rather than a computer containing 3 billion nucleotides of information that we hope will somehow lead us to understanding the junk.

In conclusion, many people in biomedical science feel that this project needs serious reevaluation. The mapping is a repetitious, quasi-industrial program, which may indeed benefit from and need central organization. But whether it deserves the scale of funding that it now has in competition with other things, is not so clear.

However, let me read the comments of Sidney Brenner, a most distinguished molecular biologist from Cambridge, England, in a CIBA conference last year, in a volume on human genetic information. He said.

We do not need committees to decide how we are going to map the human genome. Let everyone do their own thing, and the collections of DNA can be cross-referenced by probes. My prediction is that the project will be done in the form in which science has always been done: in the form of trade goods which people will barter.

And the goods are materials and information.

So it is not obvious that the activities other than mapping and sequencing need benefit from central direction at all. Looking at sequencing human regions of interest, or sequencing the whole genome of E. coli, are clearly very worthwhile jobs, but one did not need a human genome project to have support for such activities. The question is whether they should be sequestered from competition with other RO-1s as individual research projects.

The reason why this is particularly important is that in the minds of many biomedical researchers today, if we try to accumulate as rapidly as possible the descriptive information on the sequence of the human genome, and if doing so occurs at the expense of experiments in other areas, it could be counterproductive. For some of the experiments in the other areas may actually shed more light on the genome than blind sequencing, because they will have defined functions which will then move the investigator to identifying the genes. Our ultimate goal is to understand the genome, and not just to collect facts in the hope that they will be useful.

I believe the point of view that I am representing, for a good many people, is that the project should be reevaluated with the help of leaders in a variety of fields that all are using molecular genetics—but in the approach going from the functions toward the gene sequence, rather than the other way around.

I will close by saying it is extremely uncomfortable for me to be in this position. I have the highest regard for my old friend Jim Watson and for the outstanding group of people he has assembled. But at the same time, I recognize that each of us naturally thinks that his field is the most exciting in the world. The issue is how best to have an evaluation of whether this is or is not the most cost-effective approach toward the goal that we all share.

[The prepared statement of Dr. Davis follows:]

Testimony before Senate Subcommmittee on Energy Research and Development, July 11, 1990

By Bernard D. Davis, Adele Lehman Professor of Bacterial Physiology Emeritus, Harvard Medical School, Boston, MA 02115

When techniques for sequencing segments of DNA became available it seemed self-evident that the most valuable material to analyze was the regions that could be associated with a function or a disease. More than 95% of the human genome did not seem interesting to explore in detail because it does not code for the kinds of functions that we can recognize, and so it is temporarily called "junk". A few years ago, however, it was proposed that systematic sequencing of the entire human genome was now feasible and should be regarded as a major challenge.

This human genome program (HGP) had an unusual origin. It was not initiated by a committee of molecular geneticists dealing with a pressing need, or by the major biomedical funding agency, the NIH. Instead, it was advanced by an administrator in the Department of Energy (DOE), convinced that with the powerful tools of molecular biology it was now time to introduce centrally administered "big science" into biomedical research.

The idea quickly developed strong political appeal. Sequencing the entire human genome was as definite and highly visible as putting a man on the moon: it promised large benefits for human health and for our understanding of human biology; and it was claimed to be more efficient and cheaper than reaching the goal eventually by piecemeal sequencing. The NIH was initially not supportive, but when the program proved to be inevitable it became

the logical major partner. The HGP has now acquired a distinguished leader and set of advisers, and funding has grown rapidly.

Meanwhile two important changes have led to growing concern in the biomedical research community, building on an initial uneasiness about starting "big science" in their area. First, recent cuts in the funding of grants in other areas have drawn attention to the problem of competition from the HGP. Second, within the HGP the aim of starting to sequence the human genome has been replaced by a very different plan; and even though much of this involves kinds of work that would be going on even if there were no HGP, the program has inherited a high level of support, and a centralized mechanism of funding, from the initial plan. These changes suggest the need to reevaluate the HGP.

The Crisis in Research Funding

Since concern over competition of the HGP with other research funding has focused primarily on the NIH, the issue might be considered beyond the purview of a committee examining the DOE. But the two parts of the HGP are closely intertwined in their goals, and a broad perspective on how best to fund biomedical research would have to take both into account. I will therefore briefly review the current problem with NIH grants.

NIH Study Sections consider two kinds of investigator-initiated applications: new projects, and "competing renewals," i.e. applications for renewal of grants whose committed period ("non-competing renewals") has expired. Within the past few years the combined number of such grants funded annually has fallen from over 6000 to 4600, and among the total grants approved by Study Sections

the fraction funded has fallen from over 40% to less than 25%. Indeed, some Institutes have dropped this year to 15% or less. Study Sections thus face the depressing prospect of virtually tossing a coin to choose among scientists with a continuing record of distinguished achievement, and promising beginners are even more at risk. While many factors contribute to the changing number of grant awards, there is without question a real decline in the support of research, with appropriations failing to keep pace with increases in its cost and in the number of excellent applications. The conclusion seems inescapable that far too many excellent scientists are not being funded.

The consequences are far-reaching. Apart from the valuable research that does not get done, the continuity of the research enterprise, so essential for its effectiveness, is being disrupted. Moreover, bright students are being discouraged from seeking careers in science. The last effect is particularly important, at a time when the loss of interest of our youth in science, and their poor performance in international tests in science and mathematics, promise a continuing decline in our country's preeminence in science and technology..

In principle the HGP should not be part of the problem, for it was initially presented as an exciting opportunity for which Congress would be happy to provide additional money. But even though NIH officials maintain that it is still not competing, that cannot be proved. Although the HGP is listed as a separate line item in the budget for biomedical research, the structure of that budget does not reflect the psychological elements that inevitably

forces Congress, especially in times of stringency, to focus most sharply on the total.

It is thus hard to doubt that the human genome initiative is competing with the initiatives of investigators in untargeted areas. And the scale of the potential competition is not negligible. The President's budget for next year recommends a total of $7,929 million for the NIH, with $943 million for new and competing grants (from which over 60 million is targeted for grants for AIDS and the HGP) and $3,231 for non-competing grants. Hence the planned future annual total for the HGP, $200 million, would be about 5% of the amount allocated by NIH for untargeted research in all areas of the biomedical sciences.

The perception of competition on this scale is engendering bitterness in the research community. But a deeper cause for the concern is doubts about the scientific justification for the present scale and status of the HGP.

First, many are not convinced that a crash program for analyzing the structure of genomes will advance either health or the life sciences, for many years to come, as much as studies of specific physiological and biochemical functions and their abnormalities.

Second, in contrast to some areas of physics, which require extremely expensive facilities, biology does not have an obvious need for "big science." Our country's spectacular success in this area has depended much on the remarkable social invention of wide support of independent, investigator-initiated, peer-reviewed research. Many biologists fear that the precedent of the HGP will weaken this tradition.

A third concern is more political. Should this country take on a disproportionate part of the cost of a world-wide scientific problem, especially when money for science has become so tight? And is there not the added risk of generating international resentment over our hegemony, rather than appreciation for our generosity?

To judge these arguments we must consider the altered content of the HGP, and whether its different parts all need its centralized approach.

The New HGP

When a National Research Council committee appraised the initial HGP in 1986 it recognized that starting to sequence three billion nucleotides, at a cost of over $5 each, would be quite impractical. It recommended a very different program, which would postpone systematic sequencing for at least 5 years and would concentrate instead on several other activities. These included developing a map of identifiable short sequences, which would make it much easier to locate any new human disease genes or other genes; sequencing human DNA regions of interest; developing much more economical procedures for sequencing; developing systems for effectively storing and accessing the massive data; and studying the genomes of other organisms, ranging from *E. coli* to the mouse (whose genome would be just as expensive as that of humans to map or sequence).

These recent additions to the HGP are all scientifically sound. In particular, going beyond humans to these other organisms makes a great deal of sense, because they can be used as experimental models for human functions and disorders, and we will need experimental

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approaches to solve the most challenging problems. These include moving beyond one-gene traits to polygenic ones (those in which many genes contribute); elucidating the mechanisms by which a fertilized egg cell develops into an organism; elucidating the molecular basis of information storage and processing in the brain; and acquiring insight into the functions of the enormous amount of so-called "junk" DNA in higher organisms.

Nevertheless, the extensive changes in the new HGP mean that it has moved far from the initial dream. Indeed, most of it, except for the centralized plan for mapping, differs only in mechanism of funding, and in scale, from what we would be doing if the concept of an HGP had never arisen. If these activities were to be proposed as a novel program today it seems doubtful that they could generate the strong political appeal of the original proposal.

The Multiple Goals

To evaluate the justification for the present program we must look at its major components separately.

Mapping signposts along the road clearly will be very valuable. It will help to locate genes responsible for monogenic (single-gene) diseases; and eventually it will help with the much larger number of genes involved in various polygenic traits -- including most diseases, as well as the interesting physical and mental traits of individuals. Moreover, because finding the locator sites for the map is not itself very interesting, this part of the HGP evidently requires a centralized, quasi-industrial organization rather than conventional grants aimed at more creative discoveries. However, decisions about its scale of support should recognize certain limits

to its payoff. Most monogenic diseases are rare: and genes of other classes will probably be studied mostly in experimental animals, which seem unlikely to be mapped extensively.

Another goal of the HGP, the systematic sequencing of the entire human genome (now postponed), presents deeper problems. First, even if future automation should bring the cost per nucleotide below $1, the effective storage and retrieval of the 3 billion units of information will also be costly, and the total final estimate of $3 billion and 15 years is very much a guess.

A more fundamental question is whether identifying the last nucleotide in a human genome really has deep scientific value, apart from its public relations impact. Sequencing the much smaller genomes of a few viruses has been a gratifying milestone, but it has not obviously added a great deal to what had already been learned from the study of specific regions. It is even harder to see how a complete sequence could be useful for understanding the organization of the huge human genome: the dimensions are wrong, like viewing a painting through a microscope. In the genome knowledge at these dimensions will be valuable only within its functional units, each constituting a short region -- just as we need to know the complete sequence of the amino acids in a protein in order to understand its 3-dimensional structure and its function.

It thus appears that the best way to understand the genome is to continue to identify and sequence regions that can be linked to function. For this purpose it is straightforward to proceed from a known protein to its gene. The reverse process is also effective: locating the gene responsible for a disease of unknown mechanism, by

its linkage to known markers in the genome, and then using the sequence of that gene to help to identify the mechanism of the disease. An increasingly refined map of the genome is making this "reverse genetics" much easier. In a third approach, blind sequencing of the genome can also discover new genes, by recognizing a sequence with the characteristics that suggest coding for a protein; but this is not an efficient process. On the average it would be necessary to plow through 1 to 2 million "junk" bases before encountering an interesting sequence; and then finding its unknown function would also be difficult.

To be sure, it may be necessary to start from sequences in approaching one of the largest challenges: identifying the unknown functions that almost certainly exist in much of the "junk" DNA. But the answers seem likely to come from detailed study, including experimental manipulation, of small samples of the genome; it is hard to see how knowing the whole sequence would help.

For these several reasons it is perhaps no great loss that the goal of systematic sequencing has been postponed. When it is reevaluated, five years from now, it may well come to seem quite unimportant.

Among the other activities of the current HGP the research on techniques clearly overlaps with the goals of mapping and sequencing. However, the HGP mechanism of funding may give this research an unwarranted advantage over other kinds.

Finally, the other major activity, sequencing of interesting regions in humans or in lower organisms, does not have any obvious need for centralized organization, or obvious justification for insulation from competition with other kinds of research.

Conclusions

Although all the goals of the HGP, except for the complete sequencing of the human genome (now postponed), are clearly worthwhile, there is widespread concern over the present status and plans of the program. There are two reasons: its competition with other research funds at a time of financial stringency, and doubt that its scientific benefits justify its rapid expansion and its organization in the pattern of "big science." The dissatisfaction is clearly widespread: a large majority of my departmental faculty have endorsed for publication a statement very similar to this one, and with no dissenters. The HGP may therefore need reevaluation.

In any such reevaluation there would be no difficulty in justifying a centralized organization for the mapping, and probably for the research on methods. However, it is not obvious that these activities justify support for the HGP at a level equivalent to over 5% of all other biomedical research. The other main activity, sequencing regions of interest in various organisms, does not appear to need centralized organization, and its grant applications might be judged more equitably if they were fitted into the general program of investigator-initiated research.

In this connection, a reevaluation should recognize that excessive competition by the HGP could interfere with reaching its own goal, because investigations in many areas of research can lead to DNA regions of interest. The fundamental goal is to understand the human genome and its products, and not to sequence the genome because it is there. A shift of funds from the HGP to the general support of investigator-initiated research could advance this goal.

Senator DOMENICI. Thank you very much, Doctor.

Let me make the following observations for the record. I would be pleased to send these numbers and facts to you for dissemination among your biomedical associates: 1985, NIH, number of grants, 6,247; 1990, 4,600.

On the other hand, in between that period of time, at the suggestion of the scientific community of the United States, the RO-1 grants were increased in longevity by almost a year. And the average size of the grant was increased from $147,000 to $203,600. So that the Federal Government's commitment in dollars, excluding any genome appropriation, in 1985 was $5.145 billion. In 1990 it was $7.516 billion.

Now it is obvious that the number of grants have fallen, but the funding has increased by 40 percent, if my arithmetic is right, during that period. Dr. Wyngaarden, former director of NIH, and others, attribute this primarily to the size of the RO–1 grants increasing from $147,000 to $203,600, and the lengths of the grants increasing from 3.4 years to 4.3 years.

So it is very difficult, Dr. Davis, for me to explain how you can blame the genome initiative for the drop in the number of grants when last year with genome at $60 million it made up less than 1 percent of the entire $7.5 billion at NIH.

And frankly, I can give you some other comparisons.

You do not know me very well, but I am a staunch advocate of science for the United States, and I am on your side in trying to do everything humanly possible to excite young people about science. In fact, I believe that America's downfall as a great nation is probably more epitomized by the exorbitant increase in the number of lawyers per year in America and the tremendous diminution in the number of scientists, including Ph.D.s in math and physics. I am almost sufficiently confident of that.

I believe the continued upward movement of lawyers on this end and downward movement of scientists on this end is more of an economic indicator of our future, which is negative, than anything else I have found. And I happen to serve on most of the committees that look at economic issues.

But I am thoroughly amazed, Doctor, at how the biomedical community could oppose this project. I am absolutely amazed at how you could do that. It is obvious that biomedicine cannot run in this field alone. I mean the obvious interdisciplinary requirements for capitalizing on technology and other science, when you merge them, is, for me essential—and my science expertise is very limited, my first degree was in math and chemistry and I taught in a public school for one year 39 years ago, and then I did what I have just described one should not do, I went to be a lawyer. And then I came here.

Nonetheless, I cannot conceive that this small amount of money for this project over the next five years, $200 million a year, could conceivably be opposed by the biomedical community of this country. And I would almost take you up on your challenge to ask a diversified group of scientists. And we surely would not just ask biomedical scientists to evaluate this. If it has not been done by the group, I would be very willing to have another group look at it.

I cannot believe that you are going to insist on business as usual in this field. It is beyond my comprehension, I repeat, beyond my comprehension.

And, Doctor, let me suggest that if we talk about—and I do not like the word, but you all invented the word—junk, and I wish I could pick another one, but you cannot sit here and tell me that in all of the research that is going on with the marvelous individual investigators, and of which you would like to fund more and they will solve this problem. You cannot tell me that there is not more than $200 million, that if we even asked you to go look, you would say probably went for naught.

I did not even call it junk. I just said it did not get us anywhere.

People had a lot of fun. Scientists had a lot of exciting mental activities. But it is inconceivable that out of $7 billion in grants in this very heralded RO-1 peer review approach, and now it has been four and a half years without intervention, that there is not at least $200 million or $300 million that even one as dedicated to that field as you are could not go out there and look at and say, maybe we do not have to do this.

So I am not saying that. I am not saying go out and throw out some. I am merely suggesting that there are too many scientists in other fields that are using hardware and new technology and new techniques that support this as a tool, that I cannot believe that you really oppose it. And I wish we were in a position where all you would say about it is we think we need more money, but we also think this is a good program.

Now maybe you are saying that, but I have not heard it yet.

Dr. DAVIS. What I was said was that I believe that all the goals of the program are excellent. I am certainly not opposed to incorporating the powers of modern technology and high-powered computing, the kind of thing that Lee Hood is doing, into biology. The question of trying to decide which particular projects that are being funded are not worthwhile, as Dr. Watson already said, it is impossible to know where the diamonds are. If you knew where the diamonds are, then you could fund much less, and science would go ahead much better.

The problem is I would urge you, if I were only presenting my own idiosyncratic point of view, I would feel properly chastened, but I would urge you not to underestimate the extent of unhappiness in the biomedical community over this issue. Let me repeat. The members of the Public Affairs Advisory Committee of the American Society of Biochemistry endorse this statement. And virtually all the members of my department and the faculty, endorse the statement that is going to appear in Science in a couple of weeks, that is virtually identical with my written offering.

There is great uneasiness over aspects of this program, and the notion that it somehow deserves to be a crash program, very generously funded, at a time when there is famine in other parts.

Now you can say this is a dog in the manger attitude. But it is not just that. There is also the failure to be convinced that from the sequence will emerge all these beautiful things that are promised. And that is why my last recommendation was that this be reevaluated by a committee involving leaders in a variety of areas that are using molecular genetics to advance their field, but also to

help decide how cost effective it is to approach the problem from one direction or from the other.

That is the heart of the issue, really. It is not a lack of mutual respect among the groups. It is a scientific issue that of course this Senate committee cannot be asked to decide.

Senator DOMENICI. Dr. Watson, did you want to comment? You are free to. You can comment from there, or you can take a seat.

Dr. WATSON. The genome project has been evaluated by several groups. One evaluation was conductd by the National Academy of Sciences. Maybe Dr. Davis can say it was biased. The National Academy that appointed a first-class committee, which came out with a unanimous opinion. Now, you can say do another evaluation and I would be willing, but I just have to say that I have listened for years to biochemists disliking DNA, and now I am hearing them say it again. In the case of Dr. Davis' department, I suspect it is a case of political orientation.

What I am trying to say is that we have had several groups evaluate the genome project. And I think if you put some things to a vote of people who are not trying to do things, they will often vote against you. At the height of the project we will be about 2 percent of the NIH butget and, Dr. Davis said this also, that is a relatively small amount. I think it will be the best 2 percent ever spent. I feel that very strongly.

I have found in my life that if you expect to get a majority of people to try and do something new, they are going to say no. They are going to want to continue just going with the status quo. The status quo is not getting us to the heart of schizophrenia. It is not getting us to the heart of manic depressive disease. Maybe we will fail, but we are going to try.

Dr. HOOD. Could I make one brief comment in regard to the National Academy committee? It is noteworthy that there were three superb scientists who were really opposed to the genome initiative. And when they went through the debating process for 18 months or whatever it was, all of them came out unanimously on the side of the genome initiative. In my own experience, talking with the people who are against this genome initiative convinces me they do not understand these fundamental issues of the basic technology development and the framework and structure we are trying to create for biology.

And so I would say if you talk to most thoughtful biologists who really understood the issue, I am not at all convinced they would be against it.

Senator DOMENICI. Well, I just was going to ask a couple of questions. I think it has been an excellent hearing. Frankly, since I am normally the one that is supposed to know all about the budget, I am rarely in a position where I can look at a program and say it is exciting enough to keep somebody like myself energized while we are busy about trying to do these difficult things, but I found one here. And I am absolutely convinced, and I do not have any hesitation in saying that we would be foolhardy if we did not proceed.

And I am going to do everything in my power to see that we fund it. I may have even been the political whoever it was that the distinguished professor talked about that got it started. Maybe I was prompted by somebody within DOE, but frankly it got me ex-

cited. And since NIH was not very interested before Dr. Watson arrived, I was ready to go with DOE running the program. And if it took that to get everybody energized, I am very, very delighted about it.

We did have a bill that would have done that. And that brought everybody to the table and got a nice agreement reached, and we did not pursue the bill. But frankly, these are the kinds of times, in my opinion, when we do these kind of things or we fall behind. And I regret that there are members of the biomedical academic community that oppose this. I clearly do. I think they are going to be the greatest beneficiaries of this program of any group around.

I believe the next generation of biomedical researchers will have tools that the group opposing it would never have on the horizon without this program.

Dr. DAVIS. May I make one more statement.

I would not want it to appear on the record that I am opposing the program. I have questioned how its scale should be evaluated relative to the scale of other biomedical research and the fiscal problems that face us. But I stated plainly that every one of the goals of this project is something about which I am enthusiastic.

Senator DOMENICI. Dr. Hood, did you have another comment?

Dr. HOOD. No. I think it has really all been said very well.

Senator DOMENICI. Mr. Raab.

Mr. RAAB. No, thank you.

Senator DOMENICI. We will leave the record open for 2 weeks, and we stand in recess, subject to the call of the Chair.

[Whereupon, at 12:10 p.m., the hearing was adjourned.]

APPENDIXES

APPENDIX I

Responses to Additional Questions

J. BENNETT JOHNSTON, LOUISIANA, CHAIRMAN
DALE BUMPERS, ARKANSAS
WENDELL H. FORD, KENTUCKY
BILL BRADLEY, NEW JERSEY
JEFF BINGAMAN, NEW MEXICO
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FRANK M. CUSHING, STAFF DIRECTOR FOR THE MINORITY
GARY G. ELLSWORTH, CHIEF COUNSEL FOR THE MINORITY

United States Senate
COMMITTEE ON
ENERGY AND NATURAL RESOURCES
WASHINGTON, DC 20510-6150

July 17, 1990

Dr. James Watson, Director
National Center for Human Genome Research
National Institutes of Health
Building 38A, Room 613
Bethesda, MD 20892

Dear Dr. Watson:

Thank you for your testimony on July 11, 1990 before the Subcommittee on Energy Research and Development on the current status of the human genome project.

As a follow-up to that hearing, I am enclosing questions to be provided for the printed hearing record. I am requesting that the answers to these questions be provided to the Committee no later than Friday, August 3, 1990.

If you have any questions concerning this request, please contact Ben Cooper at 224-7569.

Sincerely,

Wendell H. Ford
Chairman, Subcommittee on Energy
Research and Development

Enclosures

WHF:bc

POST HEARING QUESTIONS

DR. JAMES WATSON

1. Please provide for the hearing record a breakdown of your human genome project funding for FY 1988 through the President's proposed FY 1991 budget showing, at a minimum, grants to "centers" and grants for new proposals for research by independent investigators. Please provide data to place the funding of the human genome project at NIH in the context of the NIH budget for untargeted, new competitive research proposals by independent investigators generally.

2. What evidence can you cite to support your contention that the existence of a separate human genome project will provide disease therapies quicker and more efficiently than would be the case without the project? Have discoveries of genetic structure produced cures for disease to date?

3. What are the main contributors to the high cost of specific initiatives in the research NIH supports promises to reduce this cost by a factor of 10 or more? What milestones apply to this research? At what point would you decide that sequencing the entire genome will remain too costly to recommend it to Congress?

4. Describe the elements of your program that tend to ensure that Untied States laboratories and firms will retain

ownership of key genome mapping and sequencing technologies.

5. Please provide the Subcommittee with a breakdown of the distribution of the returns from an invention, software or other intellectual property developed in the course of the human genome program. Do this for the case that the innovation is made by a Federal employee, a Federal laboratory contractor employee, or an employee of a private entity collaborating with NIH. How much goes to the Treasury? How much to laboratory contractors? How much to private firms? Explain how, in each case, you believe that the taxpayers obtain a fair return on their investment in genome research.

6. Provide the Subcommittee with examples of ethical, legal or social issues associated with genome research now under study by NIH. Include abstracts or brief descriptions of the matters to be investigated in these examples, the hypothesis being tested and the expected gain from the research.

7. Testimony incorporated in the hearing record asserts that, as presently structured, the human genome project support little research that would not be supported under priorities absent the existence of the project, except that, because the genome project is growing relative to other biomedical funding, genome work of relatively lower priority receives support. How do you answer these contentions?

8. Please provide the Subcommittee with any additional remarks that you feel should be a part of the hearing record.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Assistant Secretary
for Legislation

Washington, D.C. 20201

AUG 26 1990

Mr. Ben Cooper
Committee on Energy and Natural Resources
Subcommittee on Energy Research and Development
United States Senate
Hart 312
Washington, DC 20510-6150

Dear Mr. Cooper:

Attached is the response of [redacted] Dr. James Watson, Director, National Center for Human Genome Research, NIH, to questions submitted by Sen. Ford, following the July 11 hearing on the human genome project.

If we can be of further assistance, please let me know.

Sincerely,

James Ricciuti
Deputy Assistant Secretary
for Legislation (Health)

Attachment

Post Hearing Questions

1. Please provide for the hearing record a breakdown of your Human Genome Project funding for FY 1988 through the President's proposed FY 1991 budget showing, at a minimum, grants to "centers" and grants for new proposals for research by independent investigators. Please provide data to place the funding of the Human Genome Project at NIH in the context of the NIH budget for untargeted, new competitive research proposals by independent investigators generally.

The mechanism table outlining the funding for the National Center for Human Genome Research follows:

NATIONAL CENTER FOR HUMAN GENOME RESEARCH
(Dollars in thousands)

	FY 1988 1/ Actual		FY 1989 1/ Actual		FY 1990 Current Estimate		FY 1991 President's Budget	
Research Grants	No.	Amount	No.	Amount	No.	Amount	No.	Amount
Research Proj.:								
Noncompeting			61	16,273	94	24,486	117	34,916
Admin Supp						7u0		
Competing	63	16,767	41	10,436	50	15,160	53	17,656
Subtot.,RPGs	63	16,767	102	26,709	144	40,346	170	52,572
Research Ctrs:								
Spec/comp.				300	3	7,947	9	35,738
Subtot.,Ctrs	0	0	0	300	3	7,947	9	35,738
Other Res.:								
Careers					6	401	12	850
Other	2	468	1	37	10	993	18	1,800
Subtot.,Oth	2	468	1	37	16	1,394	30	2,650
Total, Res Grants	65	17,235	103	27,046	163	49,687	209	90,960
Training	FTTP		FTTP		FTTP		FTTP	
Indiv.					50	1,242	75	1,936
Instit.					85	1,738	149	3,130
Total, Training	0	0	0	0	135	2,980	224	5,066
R&D Contracts				500	4	4,730	5	7,971
[illegible]				684		2,141		4,032
Total, NCHGR		17,235		28,230		59,538		108,029

1/ Fiscal years 1988 and 1989 are shown for comparison purposes. Funds for this initiative were appropriated to the National Institute of General Medical Sciences. The Office of the Director, NIH supported the administrative costs associated with this initiative in FY 1989.

As you can see from the following mechanism table, which lists NIH funding and NCHGR funding, a large percentage of the NCHGR funding is budgeted for investigator-initiated research project grants. This percentage is similar to the percentage the entire NIH budgets for investigator-initiated projects.

FY 1990 Current Estimate
Funding Levels
(Dollars in thousands)

	National Institutes of Health		National Center for Human Genome Research	
Research Grants	No.	Amount	No.	Amount
Research Proj.:				
Noncompeting	15,683	$3,231,848	94	24,486
Admin Supp	(469)	22,764	(14)	700
Competing	4,633	943,345	50	15,160
Subtot.,RPGs	20,316	4,197,957	144	40,346
Research Ctrs:				
Spec/comp.	625	634,938	3	7,947
Subtot.,Ctrs	625	634,938	3	7,947
Other Res.:				
Careers	1,539	104,856	6	401
Other	2,350	273,882	10	993
Subtot.,Oth	3,889	378,738	16	1,394
Total, Res Grants	24,830	5,211,633	163	49,687
Training	FTTP		FTTP	
Indiv.	1,944	50,542	50	1,242
Instit.	9,851	236,120	85	1,738
Total, Training	11,795	286,662	135	2,980
R&D Contracts	1,345	576,495	4	4,730
Intramural Research		855,947		
Other activities		327,902		
RM&S		317,713		2,141
Total, NCHGR		7,576,352		59,538

2. What evidence can you cite to support your contention that the existence of a separate Human Genome Project will provide disease therapies quicker and more efficiently than would be the case without the project? Have discoveries of genetic structure produced cures for disease to date?

The Human Genome Project is designed to produce new and improved research tools and sophisticated knowledge, in the form of maps and entire genomic DNA sequences, of the genetic underpinnings of human biology. To achieve these goals, the National Center for Human Genome Research was established as a distinct component of the National Institutes of Health. The Center's program involves a broad, generic, and centrally managed approach to the analysis and characterization of entire genomes, in contrast to the more specialized genetics programs of other institutes which focus on specific genetic diseases or basic mechanisms of gene expression.

It is unlikely that the resource that the maps and sequences represent would be developed completely, much less in a timely and cost-effective manner, in the absence of a specific genome project. Central coordination, goal setting, rapid sharing of results, and an emphasis on collaborative research distinguish the Human Genome Program from most other NIH-supported activities. Even in the short time the Human Genome Program has been in existence, it has had a positive effect on the field, resulting in progress that has been even more rapid than was envisioned two years ago.

The availability of detailed maps and complete DNA sequences will improve the ability of scientists and physicians to understand a wide variety of diseases and biological processes. In many cases this will ultimately lead to significant improvements in our ability to manage such diseases. There are various ways in which information about the basic genetics of disease will be applied.

The history of cancer research gives a dramatic illustration of how knowledge of genes can revolutionize a field. The molecular mechanisms by which cells become malignant was completely obscure until the discovery of oncogenes, or cancer genes. Although this development is too recent to have produced a cure based on that knowledge, it has led to very exciting new directions in research and to the prospect that we may one day get away from drastic surgery and chemotherapy as the only way to treat cancer.

Often, knowledge about the identity and structure of a disease-causing gene will be most rapidly applied to the development of a diagnostic test to estimate the susceptibility of an individual to a particular disease. Examples of tests of this sort that have been developed include those for Duchenne muscular dystrophy and cystic fibrosis. DNA-based diagnostic tests will allow identification of at-risk individuals earlier than other types of tests, enabling better monitoring of patients, earlier intervention, or prevention.

Knowledge of the disease-causing gene and its DNA sequence immediately gives important information about the structure of the protein product of the gene and clues to its function. Such knowledge will also allow that protein to be produced in the large amounts necessary for enzyme or protein replacement therapy, if such therapy becomes feasible. Enzyme replacement therapy is currently being pursued in a number of cases, including lipid-storage disorders such as Gaucher's disease. Large amounts of protein are also a prerequisite for structural biological studies that might lead to new therapeutic agents through targeted drug design, an approach that has recently been a stunning success in identifying a potential new drug for AIDS.

Finally, it is important to point out that in many important cases, such as schizophrenia, bipolar affective disorder, cancer, diabetes, and heart disease, the underlying genetics will be found to be complex (that is, more than one gene will found to be involved). In these cases, there is very little chance of finding all of the genes involved by standard methods. However, recent developments have led to new techniques that allow identification of several genes involved in a particular trait. These newer techniques, which have already been applied in plants, rely completely on the use of a detailed genetic linkage map. The development of such a map is one of the important goals of the Human Genome Project.

Thus, there are many ways in which the Human Genome Project will help in the development of relief from genetic disease and diseases with genetic components. Some of these approaches are already being pursued and more will be developed as more genes responsible for disease are identified, isolated, and characterized.

3. What are the main contributors to the high cost of sequencing research that NCHGR supports? The HGP proposes to reduce this cost by a factor of 10 or more. How will this be done? What milestones apply to this research? At what point would you decide that sequencing the entire genome will remain too costly to recommend it to congress?

The current cost of sequencing is estimated to be between $2 to $5 (total cost) per base pair. While sequencing at this price is too costly for sequencing the entire human genome, individual laboratories interested in sequencing small regions of biological interest have been willing to accept this cost in return for the value of the DNA sequence. DNA sequencing on a small scale is expensive because it is largely unautomated and therefore very personnel intensive. The HGP plans to invest in technology development to reduce the cost of sequencing through automation and through invention of new, and better methods for sequencing.

Reduced sequencing costs will have an impact well beyond the HGP: if researchers can sequence at a reduced cost, more of the available resources can be devoted to the study of particular biological problems and the interpretation of sequencing data.

There are two ways in which the NCHGR believes that it will be possible to reduce sequencing costs to a level that is acceptable for sequencing the entire human genome. First, we expect to realize savings as a result of economies of scale. Currently available sequencing techniques and strategies have never been tested on a scale large enough to determine if economies can be obtained that will significantly reduce the cost. Thus the NCHGR is supporting efforts, such as those in the laboratories of Dr. Walter Gilbert (Harvard University) and Dr. Robert Waterston (Washington University) to evaluate the use of current or improved methods to sequence DNAs of a million base pairs or more to assess how far economies of scale and new strategies can reduce the cost of sequencing.

Second, NCHGR is supporting a number of efforts to develop innovative new technologies, with the aim of developing faster, more accurate and less costly sequencing techniques. There are already new, promising technologies that are entering the prototype stage such as a DNA sequencing machine based on capillary gel electrophoresis and mass spectroscopy being developed under NCHGR support by Dr. Thomas Brennan at Genomyx Corporation. In addition, automation of the entire sequencing process will reduce the number of personnel needed, directly decreasing the overall costs of the project.

With respect to milestones, the HGP's five year goal is to "improve current methods and/or develop new methods for DNA sequencing that will allow large scale sequencing of DNA at a cost of $0.50 per base pair". The NIH and DOE have established a DNA Sequencing Working Group to develop specific plans to address the five-year sequencing goals and to evaluate specific efforts. This working group recently proposed the establishment of a small number of large-scale sequencing projects over the next three years that would attempt to meet the following milestones: 1) completion of the sequence of 3 million base pairs of "finished" sequence (sequence that has been determined to be accurate enough to publish) at a cost of $0.75 per base pair in the first three years and 2) attainment of a yearly rate of 3-5 million base pairs of finished sequence by the end of five years at a cost of $0.50 per base pair. With advice from the DNA Sequencing Working Group and other committees, progress toward these goals will be carefully monitored and the milestones reassessed frequently.

Given the rapid pace at which technology development is progressing at present, we are confident that by the end of five years there will be a significant reduction in the cost of sequencing. In fact, a few laboratories believe that their sequencing costs are already below the current $2 to $5 per base pair cost estimate, perhaps even below $1 per base pair. At the

end of five years, there will be an assessment of the progress achieved. At that time, a recommendation will be made as to whether to embark on the next stage of the program, perhaps sequencing several chromosomes, or whether continued technology development is needed to bring costs down further.

4. Describe the elements of your program that tend to ensure that United States' laboratories and firms will retain ownership of key genome mapping and sequencing technologies.

U.S. Industry has been a strong participant in all aspects of the Human Genome Project from the beginning. Representatives from industry sit on genome advisory committees and industrial scientists have received numerous grants from both NIH and DOE. It is expected that industrial involvement will increase as the project proceeds, especially during the phase of large-scale sequencing.

In the very near future, a specialist in technology transfer will be joining the staff of the National Center for Human Genome Research (NCHGR). The primary responsibility of this person will be to serve as a liaison to industry. In the coming year, this person will be spearheading the formulation of a strategic plan for technology transfer with respect to inventions produced by the project. A variety of mechanisms will be explored for facilitating this transfer, for improving information flow, and for identifying potential blocks to efficient transfer.

The NCHGR and the NIH Office of Technology Transfer are planning a technology transfer conference that will bring together key representatives from the biotechnology industry, pharmaceutical companies, and government. Conference panels and participants will discuss the role of government in promoting and facilitating the transfer of technology associated with the NIH Human Genome Program.

5. Please provide the Subcommittee with a breakdown of the distribution of the returns from an invention, software or other intellectual property developed in the course of the human genome program. Do this for the case that the innovation is made by a Federal employee, a Federal laboratory contractor employee, or an employee of a private entity collaborating with NIH. How much goes to the Treasury? How much to laboratory contractors? How much to private firms? Explain how, in each case, you believe that the taxpayers obtain a fair return on their investment in genome research.

The National Center for Human Genome Research at NIH funds the research activities of investigators at universities and at the DOE National Laboratories, as well as those in private industry, through its extramural grants program. In fiscal year 1990, the Center will spend approximately $56 million to support genome research and research training programs across the country. The NCHGR does not have an intramural research program but does support some projects in the intramural programs of other NIH institutes.

The American taxpayer will benefit from the medical and scientific knowledge gained from genome research, research that will lead to an understanding and eventual treatment of thousands of genetic diseases. The Human Genome Project will also serve as a stimulus to the U.S. economy, creating new jobs within the biotechnology industry and expanding the industrial tax base. The biotechnology industry in the United States is strong and innovative and considers the genome project critical for maintaining and increasing international competitiveness. Industry will benefit directly from the availability of scientists trained by the Human Genome Project, the development of new technologies, and the availability of databases that provide access to the data generated by the project. Each of these resources will be instrumental in transferring information generated by the project to industries that can develop economically and medically useful applications.

The Federal Technology Transfer Act of 1986 provides incentives to stimulate the transfer of government laboratory-developed (intramural) technology into commercial application. Cooperative Research and Development Agreements (CRADAs) serve to spell out the terms of the collaborative research effort and are intended to facilitate the transfer of federally funded research and development for use by State and local governments, universities, and the private sector, particularly small business. Patented inventions developed under a CRADA can be licensed exclusively to the participating company, with the resulting license fees and royalties being shared with the government inventor and the remainder being retained by the laboratory for technology transfer purposes.

Under NIH policy, NIH inventors receive 25% of the first $50,000 of cumulative gross royalties on a licensed invention, 20% of the second $50,000 and 15% of the royalty income over $100,000. A portion of the royalties are used to pay for the National Technical Information Service (NTIS) licensing services and to support the staff of the NIH Office of Technology Transfer. Remaining royalty funds are distributed to the NIH institute of the inventor named on a given patent application or patent. At the present time, approximately 140 Public Health Service patent and patent applications have been licensed through the NTIS and earn royalties. Total NIH royalty income from patent licensing was $1,721,279 in fiscal year 1989. Most academic research institutions license intellectual property, such as patents, under programs similar to those implemented by the NIH Office of Technology Transfer.

6. Provide the Subcommittee with examples of ethical, legal or social issues associated with genome research now under study by NIH. Include abstracts or brief descriptions of the matters to be investigated in these examples, the hypothesis being tested and the expected gain from the research

The joint NIH-DOE Ethical, Legal and Social Implications (ELSI) Working Group has identified three topics as high priority on the genome program's ELSI agenda: the clinical impact of genome research on medical practice, the risks of genetic discrimination, and the confidentiality of personal genetic data. The Center's current studies of these topics reflect the variety of approaches it supports through its ELSI program:

A. Human genome research will greatly increase the number of gene-based diagnostic and prognostic tests available to health professionals, who will continue to shoulder the primary social responsibility for regulating their use. In the face of a shortage of trained medical geneticists, the success of such testing will depend heavily on the genetic knowledge and skills of non-geneticist physicians. Thus, NCHGR-supported researchers at the Johns Hopkins School of Medicine are using social scientific techniques to evaluate the adequacy of genetic knowledge and counseling skills among American primary care physicians (pediatricians, obstetrician/gynecologists and family practitioners). Their assessment of the preparedness of American physicians for increased genetic testing will be instrumental to a second NIH-DOE supported study by the National Academy of Sciences/Institute of Medicine, aimed at producing professional recommendations for the integration of genetic services into mainstream medical training and practice.

B. The primary risk that health professionals will face in the use of genetic tests is the misinterpretation of their findings and the potential for stigmatization and discrimination that results. Out of ignorance, patients, families, and social institutions already sometimes stigmatize genetic disorders and treat their victims unfairly. This risk broadens as the genetic elements of more health problems are uncovered, and gene-based tests for susceptibilities and carrier states are developed. Thus, NCHGR is supporting several projects aimed at improving professional and public understanding of these tests and their implications. At Dartmouth College, a philosopher is leading an interdisciplinary team of geneticists and physicians in a scholarly effort to clarify genetic disease concepts and draw out the social meaning of their different interpretations. Their conclusions will complement the empirical data of the Johns Hopkins study in informing the deliberations and recommendations of the NAS/IOM to the medical community. They will also help inform public education projects, like a forthcoming NCHGR-DOE supported public television series, "The Future of Medicine," and a series of public workshops and town meetings that the NCHGR-DOE ELSI Working Group will sponsor in the coming year.

C. Beyond improving understanding, the main way to prevent genetic information from being used unfairly is to protect its privacy. Because genetic information pertains to the most personal aspects of individuals' lives--their health problems and their reproductive plans--most wish to insure its confidentiality. But genetic information almost always has implications for other people's welfare as well, including spouses, children and extended family members. The legitimate interests of insurers and employers can also be affected. As a result, the legal bases and limits of such protections, whether in the context of medical confidentiality, privacy rights, property rights, or employment and insurance law, are still unclear. Thus, an NCHGR grant to the University of Houston Health Law Center is supporting a project commissioning studies from experts in each of these legal areas, assessing their applicability to the control of genetic information. The results of these studies will be presented at a national conference in March, 1991, which will produce recommendations for policy-making on this topic.

7. Testimony incorporated in the hearing record asserts that, as presently structured, the Human Genome Project supports little research that would not be supported under priorities absent the existence of the project, except that, because the genome project is growing relative to other biomedical

funding, genome work of relatively lower priority receives support. How do you answer these contentions?

The National Center for Human Genome Research (NCHGR) was established at NIH in recognition of the fact that the research required to achieve the goals of the Human Genome Program is distinct in scope and objective from that supported by other NIH components. Accordingly, most of the research projects supported by the NCHGR are conceptually different from those supported elsewhere at NIH in that they address the systematic mapping of whole genomes and systematic technology development based on specific goals established in concert with the scientific community. The goal is to develop a generic resource for biomedical researchers. The kind of research supported by the Human Genome Program was, in fact, not supported by NIH in any significant way prior to the initiation of the project.

With respect to the question of scientific merit, the research projects that have received support under the Human Genome Project have been of very high quality. Among the participants in the project are outstanding scientists who are leaders in their fields. They have been attracted to the project because of the enormous scientific excitement it has engendered and the potential it represents. Many younger scientists have been attracted to it for the same reasons. In fact, 28% of the genome grants have gone to younger investigators.

Applications for genome research projects are treated no differently than any other application for NIH research support. They are subjected to the same kind of peer review, by both a committee (study section) of technical experts and by a national advisory council. The results of these reviews provide the primary basis for funding decisions by the National Center for Human Genome Research. In general, only very highly rated applications have been funded.

A handful of applications that represent novel, high risk, or controversial approaches have also been supported after due consideration by the national advisory council. Even though they might not have fared well in the regular NIH programs, the council and the staff of the NCHGR considered them to have potential for very high payoff to the human genome program. In this regard, the Human Genome Project has addressed an issue that NIH has been criticized for elsewhere, namely too conservative an approach to funding decisions and a lack of willingness to support less obvious approaches to particular scientific issues.

If the ambitious goals of the Human Genome Project are to be achieved, willingness to take such risks in return for the possibility of major advances will be necessary. Overall, the award rate for applications to the human genome program has been comparable to that of other NIH institutes.

Additional Questions

8. Dr. Watson, your critics have questioned the rationale for the need to sequence the entire human genome, especially since 97% of human DNA is considered to be "junk." Why should the taxpayers of this country subsidize the sequencing of junk DNA?

The term "junk" is a euphemism. Unfortunately, it is misleading. It is true that only about 3% of human DNA is "coding sequence," that is, it contains the specific instructions for making proteins. However, the term "junk" implies that the remaining 97% of the DNA is non-functional and this is certainly not true.

Human DNA contains an extraordinarily complex system of instructions that determine at what time during development, and in what tissue, specific genes are turned on and then turned off. The importance of the precise control of gene expression is clearly illustrated by the diseases we know as cancer, which represent what happens when certain genes are turned on or turned off at inappropriate times and in appropriate places. We are only beginning to decipher the so-called "control sequences" in the DNA of higher organisms. Therefore, we do not know how much of the remaining 97% of DNA is necessary and what it does. I believe that analysis of large regions of the human DNA sequence or the sequences of the DNA of several other organisms will be vital to our developing a thorough understanding of all of the functional components of the human genome, not just the coding sequences.

Finally, if I may be allowed an analogy. It was only fifty years or so ago that most biologists, if they knew anything at all about DNA, were convinced that DNA was uninteresting because it was composed of only four sub-units and was therefore so simple in terms of the chemistry of the day that it could obviously not contain any information. I think that is illustration enough of the need to retain a healthy respect for what we don't know.

9. The work involved in achieving the goals of the Human Genome Project has been described as dull and boring. Why should this sort of effort be supported in preference to what these same individuals describe as more stimulating and exciting research?

With all due respect, I believe that this criticism misses the point. In truth, most of the actual work in any laboratory is routine and repetitive, but that is not what is of importance. The excitement and the significance lies in the data generated by the laboratory work. This will certainly be true of the results

of the Human Genome Project because there can be nothing more exciting than what we will be producing, the basic chemical blueprint of life.

It is demonstrably the case that many top-notch scientists have been attracted to work on the Human Genome Project. Some have completely devoted their laboratory's efforts in this direction, while others have begun significant amounts of mapping and/or sequencing to complement the functional gene analysis that is also going on. The scientific meetings held in the past two or three years on the subject of genome analysis have been among the most interesting that I have attended. There is momentum and excitement in this field at the moment and it's clearly not because this is boring work!

10. Is $3 billion a reasonable cost to pay for the human genome? How do you know that it can be done for that amount of money?

Yes, it is reasonable. In fact, per unit of information, it is cheap. In the absence of the project, we would get some, or even much, of the information in the long run (although if we continue to do it in the current piecemeal way, it is unlikely that we will ever get it all). But it will be at a much higher overall cost if pursued in the current fashion. By organizing, we can get more bang for our money and help the scientific community use their research dollars more effectively because these funds are currently going to mapping and sequencing by relatively expensive approaches.

The figure of $3 billion was arrived at by assuming that we could bring the cost down by a factor of ten or more from the current cost, either by improving current techniques or by developing new technology. This is not an engineering project, whose costs of labor and materials are fixed and going up all the time. In biology, you can use your ingenuity and the infinite cleverness of nature to develop better, faster, and cheaper methods for doing things that, when first discovered, are cumbersome and expensive. This has happened over and over again in the history of our science. As an example, look at nucleic acid sequencing. The first sequence determined, that of an RNA, took a team of scientists many years to decipher a sequence of 100 base pairs. Now a graduate student can determine 8,000 base pairs of DNA sequence in a single day.

When we began the project, we had faith that improved capability and concomitant cost reduction would happen again. I am gratified that our faith is already being rewarded. I believe that $3 billion is a very realistic target and our strategy is based on meeting that target or doing it even more inexpensively, if possible.

11. Many scientists believe that centers support research that is not as high quality as that supported by individual grants. Why do you propose to set up centers?

I am a great supporter of investigator-initiated individual grants and plan to continue to devote a large fraction of genome money to this mechanism, as we have done since the inception of the project. However, some kinds of research are properly supported by other mechanisms and I don't believe that we should be driven by mechanism. Our task is to accomplish the goals of the program, using all the tools available to us as a government agency.

To accomplish the goals, we believe that it is essential to establish interdisciplinary teams of investigators to address some objectives on a large scale. The key point is the concept of the interdisciplinary team. While some aspects of the development of technology for automation and scale-up of mapping and sequencing are appropriate for single investigator projects, others are not. Thus, I believe that a balanced portfolio, comprised of both single investigator grants and larger, multi-investigator projects is the approach of choice to address the NCHGR mission.

At the same time, I will not tolerate poor quality in the centers. Only outstanding research, as determined by the peer review process, will be supported. After awards are made, the performance of the centers will be watched closely and those that do not fulfill their initial promise will not continue. In addition, an important activity of the NIH centers will be the interaction with and support of the efforts of individual investigators outside the center, through collaboration and outreach activities such as the supply of materials and data. I believe that once we have some centers under way, the community will see that they are beneficial.

12. The Human Genome Project is consistently spoken of as big science and is lumped together with other programs, such as the Space Station and the Superconducting Supercollider, in the debate over big science vs. little science. Do you agree that the Human Genome Project is big science and, if so, is that appropriate?

No, I do not agree--even though I really do not know what the definition of "big science" is. Even though we speak of a single "Human Genome Project," in reality the program is a collection of individual and collaborative research projects. The largest single project I envision within the program is a center grant, which might be as much as $3 - $5 million per year in one

location (total costs). Certainly this is larger than the average NIH grant, but there are many NIH-supported research projects, such as single clinical trials or individual cancer centers, that are as large. Currently, the work is widely distributed; we fund grants in 29 states. I expect that this mode of organization will be necessary for most of the project's lifetime. If a catchy characterization is needed for this, I think it would be more appropriate to consider it to be "big little science "

To my mind, there is another important feature of the Human Genome Project that clearly distinguishes it from projects that legitimately fall under the rubric of "big science." The product of the genome project is not an instrument that must be completely finished in order to serve its intended use. Rather, all of the achievements of this program are incremental and useful in and of themselves. For example, a human genetic map exists right now and is an essential research tool, even in its relatively crude state. Our goal is to increase the number of markers on the map by two to four times. But, even if for some unlikely reason it turns out that we cannot, that we can only increase the number by 50%, the resulting map would still be considerably more useful than the map that we now have. In other words, each time a single marker is added, the quality of the product is improved. Thus, we will not have to wait fifteen years before the benefits of this project begin to be realized. They have already begun.

J. BENNETT JOHNSTON, LOUISIANA, CHAIRMAN
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United States Senate
COMMITTEE ON
ENERGY AND NATURAL RESOURCES
WASHINGTON, DC 20510-6150

July 17, 1990

Dr. David J. Galas
Associate Director
Office of Health and Environmental Research
Office of Energy Research
Department of Energy
Washington, D.C. 20585

Dear Dr. Galas:

Thank you for your testimony on July 11, 1990 before the Subcommittee on Energy Research and Development on the current status of the human genome project.

As a follow-up to that hearing, I am enclosing questions to be provided for the printed hearing record. I am requesting that the answers to these questions be provided to the Committee no later than Friday, August 3, 1990.

If you have any questions concerning this request, please contact Ben Cooper at 224-7569.

Sincerely,

Wendell Ford

Wendell H. Ford
Chairman, Subcommittee on Energy
Research and Development

Enclosures

WHF:bc

POST HEARING QUESTIONS

DR. DAVID GALAS

1. Please provide for the hearing record a breakdown of your human genome project funding for FY 1988 through the President's proposed FY 1991 budget showing, at a minimum, grants to "centers" and grants for new proposals for research by independent investigators.

2. What evidence can you cite to support your contention that the existence of a separate human genome project will provide disease therapies quicker and more efficiently than would be the case without the project? Have discoveries of genetic structure produced cures for disease to date?

3. What are the main contributors to the high cost of specific initiatives in the research DOE supports promises to reduce this cost by a factor of 10 or more? What milestones apply to this research? At what point would you decide that sequencing the entire genome will remain too costly to recommend it to Congress?

4. Describe the elements of your program that tend to ensure that Untied States laboratories and firms will retain ownership of key genome mapping and sequencing technologies.

5. Please provide the Subcommittee with a breakdown of the distribution of the returns from an invention, software or

other intellectual property developed in the course of the human genome program. Do this for the case that the innovation is made by a Federal employee, a Federal laboratory contractor employee, or an employee of a private entity collaborating with DOE. How much goes to the Treasury? How much to laboratory contractors? How much to private firms? Explain how, in each case, you believe that the taxpayers obtain a fair return on their investment in genome research.

6. Provide the Subcommittee with examples of ethical, legal or social issues associated with genome research now under study by DOE. Include abstracts or brief descriptions of the matters to be investigated in these examples, the hypothesis being tested and the expected gain from the research.

7. Testimony incorporated in the hearing record asserts that, as presently structured, the human genome project support little research that would not be supported under priorities absent the existence of the project, except that, because the genome project is growing relative to other biomedical funding, genome work of relatively lower priority receives support. How do you answer these contentions?

8. Please provide the Subcommittee with any additional remarks that you feel should be a part of the hearing record.

Department of Energy
Washington, DC 20585
August 17, 1990

The Honorable Wendell H. Ford
Chairman
Subcommittee on Energy Research and Development
Committee on Energy and Natural Resources
United States Senate
Washington, D.C. 20510

Dear Mr. Chairman:

On July 11, 1990, Dr. David J. Galas, Associate Director, Office of Health and Environmental Research, Office of Energy Research testified before your subcommittee on the current status of the human genome project.

As a follow-up to this hearing, you requested certain information be provided for the record. Per your request, I am enclosing responses to your post-hearing questions.

If you have any questions, please have your staff call Fran Davis on 586-2759. She will be happy to assist you.

Sincerely,

Jacqueline Knox Brown

Jacqueline Knox Brown
Assistant Secretary
Congressional and Intergovernmental Affairs

Enclosure

34-125 0 - 90 - 6

POST-HEARING QUESTIONS AND ANSWERS

FROM THE

JULY 11, 1990 HEARING

BEFORE THE

SUBCOMMITTEE ON ENERGY RESEARCH AND DEVELOPMENT

COMMITTEE ON ENERGY AND NATURAL RESOURCES

UNITED STATES SENATE

WITNESS: DAVID J. GALAS

ASSOCIATE DIRECTOR

OFFICE OF HEALTH AND ENVIRONMENTAL RESEARCH

OFFICE OF ENERGY RESEARCH

Question 1: Please provide for the hearing record a breakdown of your human genome project funding for FY 1988 through the President's proposed FY 1991 budget showing, at a minimum, grants to "centers" and grants for new proposals for research by independent investigators.

Answer: Funding for the DOE human genome project increased from $10.7M in FY 1988 to $26.0M in FY 1990. The President's budget for FY 1991 is at a level of $45.9M. The majority of the Department's budget goes to the three centers which we anticipate will approach optimal staffing and productivity in FY 1991 with nearly a doubling in support. Support in the form of grants for research in universities and industry will also continue to increase. A breakdown of the funding will be provided for the record. (The information follows:)

FUNDING PROFILE
(IN MILLIONS OF DOLLARS)

	Fiscal Year			
	FY 1988	FY 1989	FY 1990	FY 1991
National Lab Centers	$6.1	$10.0	$15.2	$29.7
Other National Labs	1.1	1.8	2.3	4.7
Independent Investigators	3.4	5.4	8.0	10.5
Administrative & Conf.	.1	0.3	.5	1.0
TOTAL	$10.7	$17.5	$26.0	$45.9

Question 2: What evidence can you cite to support your contention that the existence of a separate human genome project will provide disease therapies quicker and more efficiently than would be the case without the project? Have discoveries of genetic structure produced cures for disease to date?

Answer: Disease therapies derive from the understanding of mechanisms revealed by molecular biology and biochemistry research. The acquisition of such knowledge is already being accelerated by research achievements of the human genome project. These include the development of new chromosome mapping and DNA sequencing strategies, and the faster and more efficient construction of high resolution physical and genetic maps of human chromosomes.

Therapies for genetic disease could be of two forms. One form of therapy, gene replacement, might result from the replacement of the defective gene with the correct one. This requires available cloned sequences of DNA. A second form of therapy, product substitution, might result by providing the affected individual with the protein product that would normally have been produced by the otherwise defective gene, or by some drug designed to correct the defect.

Validation of extensive gene replacement therapy in humans awaits society's resolution of the associated legal and ethical issues. Product substitution therapy, on the other hand, has been quite successful. For example, because of

our knowledge of genetic structure, although limited at this time, recombinant DNA-derived human insulin and growth hormone have been produced and provided to patients deficient for these gene products.

Knowledge of the DNA sequence (genetic structure) has contributed to product substitution therapy. Without knowledge of the DNA sequence, these products would have to be biochemically extracted from human or animal body fluids at high cost. Recombinant DNA clones for all of the human genes are the raw materials for both therapies. The human genome project will assemble DNA clones which contain all the human genes during the construction of the physical map and will determine the sequence of DNA subunits for these genes. The projected cost for the national human genome project, 200 million dollars per year for 15 years translates to about $50,000 per gene for an estimated 60,000 human genes. This should be compared to the often quoted cost of at least $100 million to identify and sequence the cystic fibrosis gene alone. The genome project could therefore result in a thousand-fold cost reduction.

Question 3: What are the main contributors to the high cost of specific initiatives in the research DOE supports that promises to reduce this cost by a factor of 10 or more? What milestones apply to this research? At what point would you decide that sequencing the entire genome will remain too costly to recommend it to Congress?

Answer: A recent breakdown of the costs for state-of-the-art automated DNA sequencing is quite revealing. There is a fixed cost of approximately three hundred thousand dollars, associated with the purchase of instrumentation, which has a useful life of 5-10 years. The operating costs are derived from the use of chemical reagents and labor. Even with automation, the production of DNA sequence information is labor intensive. Labor contributes to about half the operating costs and reagents contribute to the remaining costs. The DOE is working with U.S. industry to reduce both the fixed and operating costs. This research involves advances in the biochemistry of sequencing, robotic tools that minimize the amount of human labor needed, inexpensive radically new technologies that might be able to produce DNA sequences at a much faster rate such as by scanning tunneling microscopy or automated fluorescent flow cytometric system measurements, and new computer hardware and software that allows increased speed in sequence analysis (for example, the new computer chip developed jointly by DOE-sponsored work at CalTech in collaboration with TRW). A milestone for the DNA sequencing project would be to reduce the current costs of sequencing from about $3.00 per base, one of 3 billion subunits of DNA, to less

than $0.50 per base. This will allow the development of megabase (million bases) sequencing projects to test and validate new chemistries, hardware, and software. When the costs are reduced to $0.10 per base, which is our goal, large scale sequencing of the human genome can become a routine matter.

The plans for the U.S. human genome project are reviewed and updated annually by the Joint DOE-NIH Subcommittee on the Human Genome. Any significant concern over the feasibility of sequencing the entire human genome will therefore normally be considered during these deliberations. Other analyses would undoubtedly be forthcoming from the National Research Council and the Office of Technology Assessment should a serious national concern develop.

Question 4: Describe the elements of your program that tend to ensure that the United States laboratories and firms will retain ownership of key genome mapping and sequencing technologies.

Answer: Technology transfer is an important element of the DOE human genome program. Our national laboratories have people with biomedical licensing expertise assigned to work with biomedical scientists. As new concepts are defined, patent disclosures are filed, if appropriate, and software is protected by copyright. A more difficult issue is whether recombinant DNA clones or clone libraries for which genes have not yet been identified can be patented or copyrighted. The United States law in this regard is unclear. Moreover, it is not clear whether DNA sequence information is sufficiently novel to meet the patent or copyright criteria. These issues need to be resolved. In the interim, all work or products emanating from the laboratory are reviewed by qualified technology transfer personnel to ensure that the interests of the Department of Energy, the contractor managing the laboratory, and the taxpayer are protected.

Our laboratories have succeeded in transferring a number of recombinant DNA materials, electronic hardware, and computer software to U.S. industry for commercialization. The national laboratories continue to establish licensing agreements with interested industries. Similar arrangements are in effect for university-based projects using the patent offices of the respective universities.

Question 5: Please provide the subcommittee with a breakdown of the distribution of the returns from an invention, software or other intellectual property developed in the course of the human genome program. Do this for the case that the innovation is made by a Federal employee, a Federal laboratory contractor employee, or an employee of a private entity collaborating with DOE. How much goes to the Treasury? How much to laboratory contractors? How much to private firms? Explain how, in each case, you believe that the taxpayers obtain a fair return on their investment in genome research.

Answer: The University of California contract with the Department includes a formula that controls the sharing of royalties generated from DOE-developed technology at Lawrence Berkeley Laboratory, Los Alamos National Laboratory, and Lawrence Livermore National Laboratory. The University of California recently revised its patent policy in April 1990 in efforts to provide support and incentives for further productive research rather than the highest earnings for individual inventors. All three of these laboratories are active participants in the human genome project.

The inventor's share of net royalties is on a sliding scale which decreases with increases in total royalty income: 50 percent of the first $100,000 of cumulative net royalties and fees per invention, 35 percent of the next $400,000, and 20 percent of all additional cumulative net royalties. Net royalties are gross royalties and fees, less 15 percent for administrative costs, and less the cost of patenting, intellectual property protection, and licensing costs.

Laboratory contractor, Federal and private sector inventors all have the same rights. When there are multiple inventors on one invention, the total inventor royalty share is divided equally among them unless they themselves decide differently.

The 1986 amendments to the Stevenson-Wydler Technology Innovation Act, P.L. 99-502, established royalty sharing of at least 15 percent for government inventor employees. These amendments also established that acceptable uses of net royalty funds include: intellectual property administration, including the fees or other costs for the services of other agencies, persons, or organizations for invention management and licensing services; awards for laboratory scientific exchange among the government-operated laboratories of the agency; education and training of employees consistent with the R&D mission and objectives of the agency; and for other activities that increase the licensing potential for transfer of the technology from the government-operated laboratories of the agency. Any such funds not used or obligated by the end of the fiscal year succeeding the fiscal year in which they are received shall be paid to the Treasury.

As stated in Public Law 99-502, Section 14, paragraph (2), "If, after payments to inventors under paragraph (1), the royalties received by an agency in any fiscal year exceed 5 percent of the budget of the Government-operated

laboratories of the agency for that year, 75 percent of such excess shall be paid to the Treasury of the United States and the remaining 25 percent may be used or obligated for the purposes described in clauses (i) through (iv) of paragraph (1)(B) during that fiscal year or the succeeding fiscal year. Any funds not so used or obligated shall be paid into the Treasury of the United States." In other words, if the royalties, after payment to inventors, in any fiscal year exceed 5 percent of the budget of the laboratory, 75 percent of such excess shall be paid to the Treasury. The remaining 25 percent may be obligated or used for the preceding authorized uses of net royalty funds. This section is reflected in the royalty language from the University of California's Lawrence Livermore National Laboratory contract patent clause as follows: "After payment of patenting costs, licensing costs, payments to inventors, and other expenses incidental to the administration of subject inventions, the balance of any royalties or income earned and retained by the University during any fiscal year on subject inventions under this or any successor contract containing the same requirement, up to any amount equal to 5 percent of the budget of the Laboratory for that fiscal year, shall be used by the University for scientific research, development, and education consistent with the research and development mission and objectives of the Laboratory, including activities that increase the licensing potential of other inventions of the Laboratory. If the balance exceeds five

percent, 75 percent of the excess above five percent shall be paid by the University to the Treasury of the United States and the remaining 25 percent shall be used by the University only for the same purposes as described above. To the extent it provides the most effective technology transfer, the licensing of subject inventions shall be administered by University employees on location at the Laboratory."

The 1989 amendments to the Stevenson-Wydler Technology Innovation Act, P.L. 101-189, extend application of the 1986 royalty provisions by providing for contractor laboratory directors to use/obligate royalty income from Cooperative Research and Development Agreements for purposes already authorized by the Act in 1986, for payment to contractor employee inventors, and for scientific research consistent with the mission/objectives of the laboratory.

For all royalty sharing, the emphasis is on returning the benefits from royalty income to the technology transfer activities of the laboratory. This is a fair return on investment because of the benefits of licensing activities that are returned to support the laboratory intellectual property activities. This benefits the taxpayer by stimulating the economy, through licenses to the private sector, and by reinforcing the research program that yields such useful inventions. However, to date, the return of net royalties to the national laboratories has been small, that is, less than the cost of supporting a staff member.

Question 6: **Provide the Subcommittee with examples of ethical, legal or social issues associated with genome research now under study by DOE. Include abstracts or brief descriptions of the matters to be investigated in these examples, the hypothesis being tested and the expected gain from the research.**

Answer: The progress of this nation's human genome project will certainly impact the scientific, medical, and biotechnology communities. Because of the unprecedented amount of detailed genetic information that will be available, the project will also impact society by calling attention to and intensifying some already existing ethical, legal, and social issues (ELSI).

The Department's genome program is looking ahead to identify and address these issues. In cooperation with the National Institutes of Health Human Genome Program, we have established an interagency working group on ELSI.

We have earmarked three percent of the Human Genome Program operational budget for ELSI activities and have begun our efforts with the following plans and actions:

- Two planning meetings of the DOE/NIH ELSI Working Group have been held and the purpose and objectives of the Working Group have been outlined.
- Research topics aimed at attaining ELSI objectives have been delineated. These topics represent issues that will be directly or indirectly affected by the results from the technical research activities of this program.

- Fairness in use of genetic information
- Impact of knowledge of genetic variation on individuals in society (insurance, employment practices, for example)
- Privacy and confidentiality of genetic information
- Impact on genetic counseling practice
- Influence on reproductive decisions
- Issues raised in mainstream medical practice
- Relevance of past uses and misuses of genetics
- Questions raised by commercialization of products
- Implications for conceptual and philosophical consideration

o First workshop was held February 5-6, 1990, in Williamsburg, Virginia, with special interest groups (labor, genetic counselors, publishers, disabled).

o Second workshop planned for fall 1990 will focus on Cystic Fibrosis as an "action model" for ELSI.

o Town meetings (public hearings) are being planned.

o Current genome grant review cycle includes ELSI component with eight preproposals submitted. Formal proposals are due August 8, 1990.

o The Los Alamos National Laboratory and the Lawrence Berkeley Laboratory Human Genome Centers have initiated pilot projects addressing ethical implications and legal questions related to applications of information from the genome program.

The gains from our efforts are expected to be the identification of the most crucial areas of social concern, the development of a legal agenda for consideration by the appropriate governmental bodies, and the education of the public before the issues become sensationalized and, therefore, highly polarized.

Question 7: **Testimony incorporated in the hearing record asserts that, as presently structured, the human genome project supports little research that would not be supported under priorities absent the existence of the project, except that, because the genome project is growing relative to other biomedical funding, genome work of relatively lower priority receives support. How do you answer these contentions?**

Answer: The human genome program was conceived in the Department of Energy to act as a catalyst for completing the mapping and sequencing of the entire human genome. To accomplish this task the program was organized into two well-defined and focused phases. In the first phase emphasis would be given to developing the biological, computational and technological tools needed by the scientific community to completely map human chromosomes and, later, to determine the sequence of DNA subunits in human DNA. The second phase would be initiated when the labor intensiveness and the cost of sequencing were significantly reduced to allow reasonable timely progress at an acceptable cost, as discussed earlier. Much new biological information and many innovative tools are being acquired, and we are now planning to begin sequencing on a modest scale some of those specific regions of the human genome known to be genetically functional. This type of research was and is being done in independent labs in universities throughout the country, but the focused program of research and development put in place by this Department is greatly accelerating the attainment of high resolution maps of human chromosomes and the

development of new computational capabilities that will allow us to manipulate and rapidly analyze the vast amounts of data anticipated from this intense mapping and sequencing effort. Only the highest quality research projects are being funded by this agency, but it is difficult or impossible to compare the relative "priority" of specific projects in different fields.

34-125 0 - 90 - 7

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United States Senate

COMMITTEE ON
ENERGY AND NATURAL RESOURCES

WASHINGTON, DC 20510-6150

July 17, 1990

Professor Martin Rechsteiner
Department of Biochemistry
University of Utah
Salt Lake City, UT 81432

Dear Professor Rechsteiner:

Thank you for agreeing to present testimony on July 11, 1990 before the Subcommittee on Energy Research and Development on the current status of the human genome project. I apologize for the sudden but unavoidable change in scheduling that kept you from participating as fully as we both would have preferred. Your prepared testimony will be a part of the hearing record.

I urge you to make the fullest use of the attached questions to expand on your views for this record. Please be assured that your comments will be made available to members of the Committee and will be considered in any action the Committee takes.

In order to be printed with the hearing, the enclosed questions should be answered and returned to the Committee no later than Friday, August 3, 1990.

If you have any questions concerning this request, please contact Ben Cooper at 224-7569.

Sincerely,

Wendell Ford

Wendell H. Ford
Chairman, Subcommittee on Energy
Research and Development

Enclosures

WHF:bc

POST HEARING QUESTIONS

PROF. MARTIN RECHSTEINER

1. How wide is the opposition of the biomedical and genetics research community to the human genome project -- as it is presently structured? What evidence can you give of the extent of this opposition?

2. What evidence can you give to support your contention that the conventional approach to genetic research will provide disease therapies quicker and more efficiently than will be the case with the current program, including the human genome project?

3. Your position appears to be that the National Institutes of Health should not have a separate program aimed at mapping and sequencing the human genome. Do you object to the Department of Energy having such a program? What role do you believe DOE should have in genome research?

4. Please provide the Subcommittee with any additional remarks that you feel should be a part of the record of this hearing.

THE UNIVERSITY OF UTAH

July 23, 1990

Mr. Ben Cooper
C/O United States Senate
Committee on Energy and Natural Resources
Washington, D.C. 20510-6150

Dear Ben:

Question 1 is really difficult to answer--obviously it would take a poll of U.S. bioscientists to get firm answers. However, I note from a recent Science News and Comment piece (see enclosed) that even HGP boosters admit they "have a major PR problem." I take that to mean many share the critics' views.

Question 2: This is a simple one. No gene sequence has yet produced an effective therapy. I challenge the HGP boosters to provide a single example. Clearly these sequences may someday help formulate strategies for therapeutic intervention. But, and this is an important but, any rational health program targets the major diseases. Already genes for the three major genetic diseases--cystic fibrosis, muscular dystrophy and now neurofibromatosis--have been located by traditional N.I.H. sponsored projects. Cancer genes reveal themselves easily--what is the next major genetic disease whose gene should be located? There are at best a handful.

The HGP proponents talk about 3,000 disease genes. Most afflict such small numbers of people that they pale in comparison to the health problems caused by heart disease, cancer and substance abuse.

The N.I.H. has already taken this mapping approach to its logical conclusion. The extra effort in sequencing, refined mapping, etc. will largely be WASTED when one considers therapies as I stated. We need to know how to repair biological machines; we don't need rooms filled with blueprints (sequences).

Question 3: I certainly believe the exceedingly bright scientists at Los Alamos should continue in research. They should simply work on smart projects (i.e., let's compete intelligently--fax, electronics, aerospace, communications, etc.).

As I stated on the last page of my written testimony--the HGP will not provide a marketable product. The immediate product, the sequences, will be given away. Where is the new industry? Where is our new economic advantage? I simply do not

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see it in any aspect of the HGP. For God's sake, lets get the physicists working on something economically important.

One last point, and this is my major message. Senator Domenici berated Bernie Davis because the HGP slice of the N.I.H. budget is only a few percent. I say--there are 100 Senators and if each pork barrels one percent, there goes that agency's budget. Simply put: If science and technology development are prey to the pork barrel, we will undoubtedly become a second-rate nation--and faster that one might imagine.

Sincerely,

Martin C. Rechsteiner
Professor and Co-Chair

Enclosure

MCR/km

J. BENNETT JOHNSTON, LOUISIANA, CHAIRMAN
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GARY G. ELLSWORTH, CHIEF COUNSEL FOR THE MINORITY

United States Senate
COMMITTEE ON
ENERGY AND NATURAL RESOURCES
WASHINGTON, DC 20510-6150

July 17, 1990

Professor Bernard Davis
Department of Microbiology
and Molecular Sciences
Harvard Medical School
Boston, MA 02115

Dear Professor Davis:

Thank you for your testimony on July 11, 1990 before the Subcommittee on Energy Research and Development on the current status of the human genome project.

As a follow-up to that hearing, I am enclosing questions to be provided for the printed hearing record. I am requesting that the answers to these questions be provided to the Committee no later than Friday, August 3, 1990. Please make full use of these questions to expand on your views for this record.

If you have any questions concerning this request, please contact Ben Cooper at 224-7569.

Sincerely,

Wendell Ford

Wendell H. Ford
Chairman, Subcommittee on Energy
Research and Development

Enclosures

WHF:bc

POST HEARING QUESTIONS

PROF. BERNARD DAVIS

1. How wide is the opposition of the biomedical and genetics research community to the human genome project -- as it is presently structured? What evidence can you give of the extent of this opposition?

2. What evidence can you give to support your contention that the conventional approach to genetic research will provide disease therapies quicker and more efficiently than will be the case with the current program, including the human genome project?

3. Your position appears to be that the National Institutes of Health should not have a separate program aimed at mapping and sequencing the human genome. Do you object to the Department of Energy having such a program? What role do you believe DOE should have in genome research?

4. Please provide the Subcommittee with any additional remarks that you feel should be a part of the record of this hearing.

BACTERIAL PHYSIOLOGY UNIT
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TELEPHONE: (617) 732-2022

1990 JUL 30 PM 1: 2

112 Ransom Rd.,
Falmouth, MA 02540.
(508)548-8903

July 27, 1990.

Hon. Wendell H. Ford,
Subcommittee on Energy Res. and Devt.,
U. S. Senate,
Washington, DC 20510-6150.

Dear Senator Ford,

Thank you for the opportunity to expand on the testimony that I presented at the hearing on July 11. 1990. My reply to your questions is enclosed.

Also enclosed is a petition that I have labeled Exhibit A. I am sending it to provide further concrete evidence for my claim of widespread concern over the present HGP, but it does not seem worth incorporating in the published record. If my reference to it in my statement (top line of p. 2.) would require that it be published, please feel free to delete that reference.

Sincerely,

B. D. Davis

Bernard D. Davis
Adele Lehman Professor of
Bacterial Physiology,
Emeritus

July 27, 1990.

Bernard D. Davis: Replies to post-hearing questions.

1. Evidence of broad opposition to the present structure of the human genome project (HGP).

(a) My testimony cited support from a large majority of the faculty members of my department, with no dissenters, and also uniform endorsement from the members of the Public Affairs Advisory Committee of the Amer. Soc. Biochem. and Mol. Biol.

(b) In the diverse research community at the Marine Biological Laboratory in Woods Hole, where I am spending the summer, the HGP is probably the most frequent topic of conversation these days, and all but one of my dozens of contacts expressed concern over the rapid expansion of the HGP. Furthermore, at a public symposium on Science and Public Policy held here last week I presented my views, following a description of the project by Dr. Elke Jordan, and it was clear that I had a very sympathetic audience.

(c) Dr. James Watson dismissed the support by my department by alleging that this dept. is well known to be politically opposed to any research on human genes. (Unfortunately this intemperate remark was not fully recorded in the transcript that I have received.) This statement would have been true for some members of the dept. 15 years ago, but it is simply not true today. Moreover, a scientist at Texas A & M University has sent me a petition, signed by 100% of the faculty of the Depts. of Bichemistry/Biophysics and of Biology, that protested the rapid growth of HGP while other kinds of research are constricted

(Exhibit A, enclosed). It seems doubtful that Texas A & M is a hotbed of left-wing agitation.

2. Conventional vs. HGP approaches to genetic research.

The heart of the HGP problem is the question whether this approach will provide therapies, and fundamental advances that might lead unpredictably to therapies, more efficiently than current conventional approaches. I hope we will see this question dissected in detail in future discussions of the project.

At present it is clear that "top-down" studies, which proceed from known functions to the gene responsible, have already given us a good deal of knowledge about the human genome. Moreover, it has become quite easy, once a novel protein or messenger RNA has been isolated, to locate and sequence its gene, and such studies are now flourishing in a wide variety of areas. In contrast, the "bottom-up" approach, starting from sequence, not only has to sequence a great deal of irrelevant DNA in order to find a region that looks as though it codes for a product. It then faces two major obstacles: identifying those parts of the gene that are retained, in the splicing of the corresponding RNA, to yield the messenger RNA that is translated into a protein; and then trying to guess what that protein might do, in what cells, and at what stage of development.

It is quite possible that in this rapidly advancing field these obstacles will be overcome. That is why I approve of the goals of the current HGP. But at present the glorious promises presented at the hearing constitute a giant IOU. Since the problem of interpreting sequences is going to be essentially

the same for all chromosomes, it is not necessary to map and sequence 24 different chromosomes in order to try to make bottom-up correlation of sequence and function more efficient. The goal of sequencing the genome is now being postponed until it becomes much cheaper, but I would suggest that it also be postponed until advances in the bottom-up approach have demonstrated that extending the sequenco to the rest of the genome will be worth the effort.

Sin do not work in this field my answer is necessarily rather general. But a recent conversation with Dr. Jack Strominger, of the Biology Dept. at Harvard Univ., reinforces my conviction. He is one of the leading investigators of the molecular biology of the histocompatibility complex, which plays a key role in the immune system, both in its normal response to foreign invaders and in its self-destructive response to our own tissues in many diseases. His studies, starting with known components of that complex, have led him also to identify not only their genes but a dozen additional genes in the same region of the genome; but he simply cannot find a way to identify the functions of these novel genes -- though he has the advantage that the search is already narrowed down to the immune system. I find this compelling evidence for the present superiority of the top-down approach to linking sequence with function.

3. DOE and NIH.

I'm afraid I did not make my position clear, if it seemed that I objected to a program at the NIH aimed at mapping and sequencing the human genome.

(a) I expressed skepticism about the value of complete sequencing of that genome, in any program (unless, as just noted, the obstacles to the bottom-up approach are overcome).

(b) I questioned whether some parts of the current program, involving sequencing of simpler genomes and research on methods, need a separate program at the NIH, but I did not object to their support by the NIH; instead, I suggested that they could be handled within the framework of the rest of the NIH grant program.

(c) Since the benefits of mapping will be seen most immediately in its contributions to the diagnosis of monogenic diseases, the NIH seems to me to be the logical organization to direct such a program. It is simply a historical accident that the DOE, looking for ways to justify or to expand its biomedical research, played such a prominent initial role in developing the HGP and now remains a major partner. On the other hand, we do build on historical accidents; and since the mapping appears to require quasi-industrial centers, I do not object to a role of the DOE in providing such centers, even though the linkage to its mission seems a bit forced.

In this connection, a witness from the DOE made two predictions about the value of the project that puzzled me.

(a) He stated that sequencing the genome was the only way to solve the major challenge of understanding those diseases or traits that depend on a number of genes rather than on a single one. However, so far our greatest success in this area has been "top-down" -- the work of Brown and Goldstein on identifying several interacting proteins (and then their genes) that

influence cholesterol transport and metabolism and hence play such a large role in heart disease and stroke. I find it hard to see how the alternative approach, which starts with sequencing a novel gene, will give any hint about the other genes whose products contribute to the same function.

(b) We were told that a major reason for DOE interest in the HGP is the failure of conventional measures of DNA damage (recognizable mutations; detectable chromosome changes) to reveal as much genetic damage in the survivors of Hiroshima and Nagasaki as had been expected. However, if mutations with detectable effects on function have not been frequent enough to detect, it is not obvious to me how knowing the whole genome sequence is going to provide tools for more sensitive tests of damage; surely one is not going to sequence entire genomes from parents and offspring in order to demonstrate mutations. Other, feasible approaches may well exist: I would simply like to know what they are, before I could consider this a justification for heavy involvement of the DOE in the project.

4. Additional comments.

In the discussion of the current claim of a crisis of funding of new grants I was disappointed that Senator Domenici minimized the problem by emphasizing the overall increase in the NIH budget, and the increased average length and size of grants awarded in recent years at the request of the scientific community. These facts are all sound, but they do not explain away the problem. For while the NIH has stated that this year 24% of approved grants have been awarded, this figure seems hard

to reconcile with the reports from colleagues in various Study Sections, who have ended up seeing much lower figures. For most Institutes the figure for this year is below 20%, which is very discouraging.

While I have expressed serious scientific reservations about some aspects of the HGP, there is no doubt that the reaction to these problems has been made much more intense by the contraction in other kinds of biomedical studies -- including many that contribute, by the "top-down" approach, to understanding the human genome. Even if the widespread perception of financial competition from the HGP is exaggerated, the harmful effect of the discrepancy in funding is real. On the other hand, if both approaches could flourish there would be much less reason for heated argument about which is likely to be the more effective in reaching their common goal: to understand the nature of living organisms and especially of humans, and to use that understanding to advance our welfare and to cure and prevent disease. The HGP would still be based on unproved assumptions about the value of the sequence, but the gamble would be more acceptable if it did not seem to be interfering with more established approaches.

In closing, I would like to reiterate my confidence in the quality of the research that will be sponsored by the present distinguished scientific leadership of the HGP. It is important that all the current goals of the HGP (apart from complete sequencing of the human genome) be supported; but the justification for its very rapid expansion is not clear. There are many equally brilliant scientists who are advancing

biomedical research in ways that promise more immediate benefits and more certain contributions to real understanding of our genome. As a practical solution, the recent recommendation of the House Appropriations Committee, that the HGP be increased slightly next year and that funds be earmarked for a large increase in R01 grants, seems very reasonable.

The deep split in the biomedical research community over the HGP is very regrettable, and it is important to try to restore normal collegiality. I therefore hope the supporters of the project will adapt gracefully to the effort of the House to place them on more of a financial par with the other branches of the biomedical sciences. In addition, presenting the project as a Mt. Everest that must be scaled because it is there, or as something that is exciting because the genome is our essence, seems less realistic than recognizing that the project aims at providing a potentially very powerful set of tools. Since to a large extent the power of these tools remains to be shown, this approach should be explored much like any promising new approach, rather than as an already established, unique set of keys to the kingdom.

A footnote on hyperbole: The statement has been published that the search for the gene for cystic fibrosis cost $120 million, and one witness at the hearing used the figure $150 million; hence the whole genome at 200 per year would be a bargain. Since I found it hard to see how the few laboratories working on this project could have spent so much, I checked with the Cystic Fibrosis Foundation and was informed that $120 million represented all that had been spent on cystic fibrosis research, by that Foundation and the NIH, in the past 20 years. Obviously the effort involved in locating the gene can represent only a small fraction of that total.

(Exhibit A)

Dr. Davis,

Here are photocopies of petitions from the Departments of Biochemistry and Biophysics and Biology. Although many faculty were out of town in early July, at meetings or on vacation, 100% of the Biochemistry faculty on board signed (17/17, with 7 faculty out of town). A similar percentage was obtained in Biology. Essentially everyone in these two departments, by far the leading biological research departments on campus in terms of funding and publications, support the thrust of the petition enthusiastically. Another petition is making the rounds of the College of Medicine, and although I do not have the completed document, all 9 faculty in town in the Departments of Medical Biochemistry and Medical Microbiology (both of which have high levels of NIH funding) signed it. This brings the TAMU total to 45, with not a single person yet approached who refused to sign.

The HuGe people may take this as evidence of the block "journeyman" vote, and if so, so be it. There are a lot of good scientists in the group.

Let me know if I can be of any help and good luck.

Ry

RY YOUNG

409-845-2087
FAX 409-845-9274

Post-it™ brand fax transmittal memo 7671 | # of pages ▸ 4

To	Dr. Bernie Davis	From	Dr Ry Young
Co.		Co.	
Dept.		Phone #	
Fax #	(518) 540-6902	Fax #	(409) 845-9274

PETITION TO SENATOR GRAMM

We, the undersigned, are your constituents and also faculty members at Texas A&M University. We want to call your attention to the Human Genome Project (HGP), the funding for which is currently under consideration before the Subcommittee on Labor-Health and Human Services-Education. HGP proponents are asking for $3 billion within the NIH budget over the next 15 years, with the goal of determining the sequence of the entire human genome. We differ in our individual estimates of the priority which should be assigned to this endeavor, although we all agree that useful information would be obtained. However, we are united in concern about the potential effects of funding HGP within NIH at a time when the resources available for non-targeted, investigator-initiated basic research are a shrinking fraction of the NIH budget. This is a real crisis for American biomedical science, especially the small grant which competes in the free marketplace of ideas and is the engine that has brought American biomedical research to world preeminence. Twenty-five percent fewer non-targeted grants are funded now than in 1980. In many areas, more than 85% of the grant proposals are being left without funds. Thus if funding HGP within NIH results in further downward pressure on the resources available for non-targeted individual grants, the crisis will be exacerbated and long-term damage done to the infrastructure and productivity of American biomedical science.

We urge that, if HGP is funded at this substantial level, its funding be mandatorily linked to a corresponding and equivalent increase in resources for basic non-targeted research. A $200 million annual sum like that requested by HGP would add about 1500-2000 grants to the non-targeted grant pool, which would be a positive step toward alleviating the current crisis. In this way, the worthwhile goals of the HGP can be pursued and we can preserve our threatened free-enterprise system of science in which good ideas have a reasonable chance for adequate funding.

Ryland Young (Ryland Young)

William D. Park (William D. Park)

James R. Wild (James R. Wild)

Gary R. Kunkel (Gary R. Kunkel)

David O. Peterson (David O. Peterson)

C. R. Benedict (C. R. Benedict)

David P. Giedroc (David P. Giedroc)

E.D. Harris (E.D. Harris)

Randall Wood (Randall Wood)

J. Martyn Gunn (J. Martyn Gunn)

A.S. Garay (A.S. Garay)

C.N. Pace (C.N. Pace)

Joseph Nagyvary (Joseph Nagyvary)

George W. Bates (George W. Bates)

Donald W. Pettigrew (Donald W. Pettigrew)

John Mullet (John Mullet)

Timothy M. Lohman (Timothy M. Lohman) (Biochemistry)

PETITION TO SENATOR GRAMM

We, the undersigned, are your constituents and also faculty members at Texas A&M University. We want to call your attention to the Human Genome Project (HGP), the funding for which is currently under consideration before the Subcommittee on Labor-Health and Human Services-Education. HGP proponents are asking for $3 billion within the NIH budget over the next 15 years, with the goal of determining the sequence of the entire human genome. We differ in our individual estimates of the priority which should be assigned to this endeavor, although we all agree that useful information would be obtained. However, we are united in concern about the potential effects of funding HGP within NIH at a time when the resources available for non-targeted, investigator-initiated basic research are a shrinking fraction of the NIH budget. This is a real crisis for American biomedical science, especially the small grant which competes in the free marketplace of ideas and is the engine that has brought American biomedical research to world preeminence. Twenty-five percent fewer non-targeted grants are funded now than in 1980. In many areas, more than 85% of the grant proposals are being left without funds. Thus if funding HGP within NIH results in further downward pressure on the resources available for non-targeted individual grants, the crisis will be exacerbated and long-term damage done to the infrastructure and productivity of American biomedical science.

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(Biology)

(Terry L. Thomas)

(Brian H. Taylor)

(Thomas D. McKnight)

(Jim Golden)

(Susan S. Golden)

(Vincent M. Cassone)

(Richard T. DeRose)

(W.M. Kemp)

(Mary K. Wicksten)

(Peter J. Rizzo)

(Ira F. Greenbaum)

(James R. Maubert)

Thomas Adams (Thomas Adams)

G Bhaskaran (G Bhaskaran)

J.C. Cakkington (J.C. CAKKINGTON)

T-C Hall (T-C HALL)

Kathryn A VandenBosch (K. A. VandenBosch)

Lawrence R Griffing (Larry Griffing)

Paul I. Welden (Paul Welden)

APPENDIX II

Additional Material Submitted for the Record

NATIONAL DOWN SYNDROME SOCIETY
666 BROADWAY
NEW YORK, NY 10012
212-460-9330 or 800-221-4602
Fax: 212-979-2873

June 18, 1990

Honorable Pete V. Domenici
United States Senate
Dirksen Senate Office Building, Room 434
Washington, DC 20510

Dear Senator Domenici,

The National Down Syndrome Society is very pleased to share with you our opinions regarding the Human Genome Initiative. We support the proposed increases in funding for this initiative, and at the same time encourage increased funding for the overall NIH budget.

The Society was established in 1979 to support research about Down Syndrome and its related illnesses of Alzheimer's disease and childhood leukemia; to promote public awareness and education about this genetic disorder; and to provide services for families and individuals with Down Syndrome.

There are more than 250,000 people in the United States who have this genetic disorder. It occurs in one in every 800 births, and eighty percent of the new parents are under age 35. This disorder is characterized by some degree of mental retardation, usually in the mild to moderate range. Everyone with Down Syndrome will have the plaques and tangles associated with Alzheimer's disease and more than 25% will ultimately exhibit the dementia associated with this illness. Leukemia occurs 40 times more commonly in children with Down Syndrome, and more than 40% of these children will be born with a heart defect. All of these characteristics relate to the fact that the person with Down Syndrome has an extra number 21 chromosome.

The National Down Syndrome Society has been instrumental in encouraging research about the number 21 chromosome. It hosts an annual science meeting on topics of relevance to Down Syndrome, and provides science scholar grant awards to young post-doctoral researchers. In 1984 the Society sponsored the first science symposium on the molecular structure of chromosome 21 which brought together world-renowned scientists to share their unpublished work in this field. This meeting resulted in new collaborations and thrust the research forward in new directions toward mapping this small but powerful chromosome. In six short years the chromosome has been mapped.

(con't)

Based on its broad involvement in the support of research, and very limited funds to carry out this work, the National Down Syndrome Society feels strongly that Congress should support the planned increases in funding for the human genome initiative. It is only with this critical government supported funding that scientists will be able to continue their work on the chromosomes to find specific answers to Down Syndrome and other genetic disorders.

At the same time the Society urges Congress to support increases in the overall National Institutes of Health budget. The present NIH funding level is dangerously low and poses a serious threat to biomedical research in the United States. Appropriate increases will enable new and on-going biomedical research projects to be carried out that do not fall within the human genome initiative, but are equally important to the understanding of disorders such as Down Syndrome. For example researching why an extra 21st chromosome occurs, i.e. what causes non-disjunction, will one day answer what causes Down Syndrome. Studying the brain and its functioning will help to unravel the learning process in people with mental retardation. These studies complement the human genome initiative, but are not part of it. They too must ~~receive~~ adequate funding so that working at the same time researchers on the human genome initiative and researchers on other specific NIH projects will find the answers that ultimately affect every one of us.

The National Down Syndrome Society urges the United States Senate not to take limited funds from one research budget for another, but to allocate sufficient funds for both components so the United States can continue to be in the forefront of biomedical research which is unraveling the answers that affect the lives of people with genetic disorders such as Down Syndrome, their families and community.

Thank you for the opportunity to share our opinion with you and members of your committee. We will be pleased to answer any questions you may have, or provide you with additional information.

Sincerely,

Donna M Rosenthal

Donna M. Rosenthal
Executive Director

3DMR167/wbh

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OSTEOPOROSIS
FOUNDATION

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GRATTAN E. WOODSON, III, M.D.

Executive Director
SANDRA C. RAYMOND

June 20, 1990

The Honorable Pete V. Domenici
United States Senator
Washington, DC 20510

Dear Senator Domenici:

Thank you for your recent letter regarding the Human Genome Initiative which undertakes to sequence and map all of the DNA in the human chromosome. I appreciate the opportunity to provide you with our views on this important scientific endeavor.

As you know, osteoporosis, is a serious public health problem that affects 24 million Americans and accounts for about 1.3 million fractures per year. Osteoporosis, characterized by an exaggerated loss of bone tissue, costs the Nation from $10 to $18 billion annually as a direct result of fractures to the hip, spine, wrist, and other bones. With the aging of the population, costs related to osteoporosis are expected to rise precipitously in the next decade.

We know that all bone goes through a process called remodeling in which part of the bone surface is dissolved and then rebuilt. Until about age 35, more bone is built than is dissolved, leading to growth in both size and density of the skeleton. At about the mid-thirties, however, the amount of bone in the skeleton begins to decline, a process which for women accelerates at menopause.

At present, we do not know the underlying cellular mechanisms that cause rapid bone loss. Nor do we understand why in some individuals that process becomes so exaggerated that osteoporosis results. Were we to identify the genes responsible for normal bone remodeling, we would be closer to identifying what occurs when osteoporosis develops.

While we enthusiastically support the work of the Human Genome Initiative, we must also reiterate our support for the entire area of basic biomedical research at the National Institutes of Health (NIH). We are concerned about a growing trend at NIH for fewer worthwhile grants to be funded and for

fewer individuals to conduct research for the Federal Government. The work done at NIH, such as the Human Genome Initiative, is work that cannot be repeated in the labs of private industry. NIH provides a unique setting to answer basic scientific questions not bound by product development. Thus, NIH represents a valuable national resource that we have failed to adequately support.

Thank you again for the opportunity to express the view of the National Osteoporosis Foundation. If I can be of further assistance, I hope you will call on me.

Sincerely,

Sandra C. Raymond

Sandra C. Raymond
Executive Director

EMORY UNIVERSITY SCHOOL OF MEDICINE
DEPARTMENT OF BIOCHEMISTRY
Woodruff Memorial Building Atlanta, Georgia 30322

June 20, 1990

The Honorable Pete V. Domenichi
U.S. Senate
Washington, D.C. 20510

Dear Senator Domenichi,

I am writing in strong support of the National Center for Human Genome Research of the National Institutes of Health. I understand there is some support to limit the proposed increase in funding for the NCHGR; a move I am in strong opposition of. The goals of the Human Genome Project will revolutionize human biology and medicine as well as provide technological development that will rival that of the early manned space program. Furthermore, the national scientific prestige and commercial implications of this project are not to be overlooked.

It is true that federal support for federally-sponsored biomedical research is dangerously low and needs immediate attention. However, I urge you not to consider diminishing support for the National Center for Human Genome Research.

I thank you for your consideration of my opinion.

Sincerely yours,

Stephen T Warren

Stephen T. Warren, Ph.D.
Assistant Professor of Biochemistry
and Pediatrics.

THE ROBERT W. WOODRUFF HEALTH SCIENCES CENTER
(404) 727-5962 FAX: (404) 727-0251

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June 22, 1990

The Honorable Pete V. Domenici
United States Senate
Washington, DC 20510

Dear Senator Domenici:

I am enclosing a copy of an article you may have missed about multiple sclerosis research. It appeared on the front page of the New York Times on May 24th. Clearly we have grounds to remain optimistic about the eventual prevention and cure of this major disabling disease of young adults.

Also enclosed is our latest bi-annual publication which addresses new and pending federal legislation of interest to people concerned about multiple sclerosis. Action Alert Special Advisory is produced for the National Multiple Sclerosis Society's more than 6,000 volunteer advocates at our 140 chapters and branches across the country.

The Society is proud of our strong grass-roots advocacy network. We attribute this to our steady emphasis on self-empowerment for each of our 400,000 members to help them reach maximum independence while research for this cause and cure for MS continues.

Until such time, the National Multiple Sclerosis Society, with its 140 chapters and branches, is here as a source of information for you and your constituents. We ask you to help maintain support for the National Institutes of Health which funds about 85% of all MS research in the United States.

Sincerely,

Martha Keys

Martha Keys
Vice President
Public Affairs

Enclosures

The National Multiple Sclerosis Society is proud to be a source of information about multiple sclerosis. Our comments are based on professional advice, published experience and expert opinion, but do not represent therapeutic recommendation or prescription. For specific information and advice, consult your personal physician.

National Foundation for
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Tel: (212) 685-3440 (800) 343-3637 Fax: (212) 779-4098

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June 26, 1990

Senator Pete V. Domenici
United States Senate
Washington, DC 20510

Dear Senator Domenici:

Thank you for your letter of June 8 in which you requested this Foundation's opinion on the Human Genome Initiative. I am happy to share our thoughts on the importance of genetics research vis-a-vis the search for a cure for inflammatory bowel disease (IBD).

Genetic and epidemiological research has determined that the major epidemiological risk factors for IBD are genetic susceptibilities, but detailed basic science investigations are necessary to pursue these clues. We believe, for example, that a principal initiative should be to establish a comprehensive cell line bank with information correlated to a DNA and serum bank. High priority should be placed on establishing cell lines from families with multiple affected cases.

Historically, cell line banks have successfully advanced our understanding of a number of diseases that have no clear-cut etiologies. For example, such a bank has established that Type I diabetes is an autoimmune disease mediated by an attack of the immune system upon the beta islet cells. Moreover, this type of diabetes has been discovered to be associated with certain gene markers. The story of cystic fibrosis is similar. After years of research accelerated by a quantum increase in research dollars, scientists have discovered the gene involved in this disease, i.e., the cause, and can now look for the cure. Those in IBD research need the resources to map the genes specifically associated with Crohn's disease and ulcerative colitis. Finding the genes that predispose to IBD is crucial to the search for the cure.

Inasmuch as the Human Genome Initiative may support genetics research in IBD, we are interested in seeing that project carried out.

I hope this information is useful to you. Please contact me if I can be of more assistance.

Sincerely,

Barbara Boyle

Barbara Boyle
Executive Director

American Foundation for the Blind

Governmental Relations Department 1615 M St., N.W., Suite 250 Washington, DC 20036
202-457-1487 FAX 202-457-1492

July 13, 1990

The Honorable Pete V. Dominici
U.S. Senate
Washington, DC 20510

Dear Senator Dominici:

This is in response to your letter seeking our opinion on the Human Genome Initiative. Our organization does not have medical expertise and is unable to comment from that standpoint.

The American Foundation for the Blind is a national nonprofit organization whose primary mission is to ensure the development, maintenance, and constant improvement of services for blind and visually impaired people in the United States.

Recognized as Helen Keller's cause in the United States, AFB works in partnership with more than 1,000 specialized agencies, schools, and organizations of and for blind people.

However, we support the Initiative because of its great potential for the benefit of mankind. A program that has the potential of identifying the gene(s) causing so many of the known hereditary diseases and of others not yet known should be a national priority. From our viewpoint if we can identify and correct the causes of diabetes we will have removed one of the major causes of blindness. One of the exciting findings in the program was announced this morning in the New York Times; scientists have isolated the gene that causes neurofibromatosis which, as you know, can cause the growth of tumors on the optic nerve. Also, researchers have, in the last few years, isolated a gene causing a rare type of familial eye cancer.

We commend you for your efforts to ensure that this valuable program is continued and properly funded.

I appreciate the opportunity to express the views of the American Foundation for the Blind. If your staff have any questions, please have them contact Glenn Plunkett who is in our Washington Office at (202) 457-1496.

Sincerely,

William Gallagher
Executive Director

WG:lg